# DETERMINANTS OF STRUCTURAL CHANGES IN THE KNEE JOINT IN A MIDDLE-AGED COHORT WITH A LOW PREVALENCE OF OSTEOARTHRITIS

by

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## Statement of Co-authorship

The following people and institutions contributed to the publication of work undertaken as part of this thesis:

### Chapter 4

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The Contribution of each author:

- HIK carried out analysis and interpretation of data, prepared the initial manuscript draft, and completed manuscript revisions.
- DA was responsible for data cleaning and management, data interpretation and drafting of the manuscript.
- LB was responsible for data analysis and drafting of the manuscript.
- JPP, JMP and their team were responsible for the measurement of femoral cartilage volume and drafting of the manuscript.
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## Chapter 9

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**Khan HI**, Aitken D, Chou L, McBride A, Ding C, Blizzard L, Pelletier JP, Martel-Pelletier J, Cicuttini F, Jones G. Reply Letter to the Editor: Knee joint replacement and individual susceptibility for progression of knee osteoarthritis and tibial cartilage volume loss: not only genes run in the family. Osteoarthritis Cartilage. 2015 Oct;23 (10):

**Khan HI**, Dore D, Zhai G, Ding C, Pelletier JP, Martel-Pelletier J, Cicuttini F, Jones G. Association between hip and knee cartilage measured using radiographs and magnetic resonance imaging: the Tasmanian Older Adult Cohort Study. Rheumatology (Oxford). 2013 Nov;52 (11):2009-15.

Pan F, Ding C, Winzenberg T, **Khan HI**, Martel-Pelletier J, Pelletier JP, Cicuttini F, Jones G. Response to: 'Does it make sense to investigate whether the offspring of people with a total knee replacement for severe primary knee osteoarthritis have a higher risk of worsening knee pain?' by Lei *et al*. Ann Rheum Dis. 2015 Aug;74 (8):e45.

Pan F, Ding C, Winzenberg T, **Khan HI**, Martel-Pelletier J, Pelletier JP, Cicuttini F, Jones G. The offspring of people with a total knee replacement for severe primary knee osteoarthritis have a higher risk of worsening knee pain over 8 years. Ann Rheum Dis. 2016 Feb;75 (2):368-73.

Pan F, **Khan HI**, Ding C, Winzenberg T, Martel-Pelletier J, Pelletier JP, Cicuttini F, Jones G. Familial effects on structural changes relevant to knee osteoarthritis: a prospective cohort study. Osteoarthritis Cartilage. 2015 Apr;23(4):559-64.

## Scientific presentation arising from this thesis

**2012**

- Association between hip and knee cartilage measured using radiographs and magnetic resonance imaging: the Tasmanian Older Adult Cohort Study. American College of Rheumatology Conference 2012 Washington DC, USA. (**Poster Presentation**)

**2013**

- A family history of knee joint replacement increases the progression of knee radiographic osteoarthritis and cartilage volume loss over 10 years. American College of Rheumatology Conference 2013 in San Diego, USA. (**Poster Presentation**)
- History of knee injury and MRI-assessed knee structure in middle and older aged adults. American College of Rheumatology Conference 2013 in San Diego, USA. (**Poster Presentation**)
- Meniscal extrusion is a better predictor of radiographic osteoarthritis change over ten years compared to cartilage volume. American College of Rheumatology Conference 2013 in San Diego, USA. (**Poster Presentation**)
- Predictors of cartilage volume loss over 10 years in a mid-life cohort. American College of Rheumatology Conference 2013 in San Diego, USA. (**Poster Presentation**)
- The clinical significance, natural history and predictors of bone marrow lesion change over eight years. American College of Rheumatology Conference 2013 in San Diego, USA. (**Oral Presentation**)

**2014**

- Natural history and clinical significance of meniscal tears in a mid-life cohort. Australian Rheumatology Association Conference in Hobart 2014, Australia. (**Oral Presentation**)
- Meniscal tracking in a midlife cohort. American College of Rheumatology Conference 2014 in Boston, USA. (**Poster Presentation**)
- Predictors of cartilage volume loss over 10 years in a midlife cohort. Australian Orthopaedic Association Conference 2014 in Melbourne, Australia **(Oral Presentation)**

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- Natural history and clinical significance of cartilage defects in a mid-life cohort. Osteoarthritis Research Society International (OARSI) World Congress 2015 in Seattle, Washington, USA. (**Oral Presentation**)
- Natural history of cartilage defects over 10 years and the role of sub-chondral bone. Bone and Mineral Society Annual Meeting 2015 in Hobart, Australia. **(Poster Presentation)**

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# List of Abbreviations

| | |
|---|---|
| 2D | Two-dimensional |
| 3D | Three-dimensional |
| ACR | American College of Rheumatology |
| AQoL | Assessment of quality of life |
| BME | Bone marrow edema |
| BMI | Body mass index |
| BML | Bone marrow lesion |
| CI | Confidence interval |
| CTX-II | Type II collagen C-terminal telopeptide |
| CV | Coefficient of variation |
| dGEMRIC | Delayed gadolinium-enhanced magnetic resonance imaging of cartilage |
| DMOAD | Disease-modifying osteoarthritis drug |
| FDA | Food and Drug Administration |
| FFQ | Food frequency questionnaire |
| FS | Fat suppressed |
| FSE | Fast spin echo |
| GRE | Gradient-recalled echo |
| HDL | High-density lipoprotein |
| ICC | Intraclass correlation coefficient |
| IL | Interleukin |
| JSN | Joint space narrowing |
| JSW | Joint space width |
| K/L | Kellgren and Lawrence |
| KOOS | Knee injury and Osteoarthritis Outcome Score |
| LF | Lateral femoral |

| | |
|---|---|
| LSC | Least significant criterion |
| LT | Lateral tibial |
| MF | Medial femoral |
| MOST | Multicentre Osteoarthritis Study |
| MRI | Magnetic resonance imaging |
| MT | Medial tibial |
| NHMRC | The National Health and Medical Research Council |
| NSAIDS | non-steroidal anti-inflammatory drugs |
| OA | Osteoarthritis |
| OR | Odds ratio |
| Pa | Per annum |
| RA | Rheumatoid arthritis |
| RCT | Randomised controlled trial |
| ROA | Radiographic osteoarthritis |
| ROI | Region of interest |
| sBMD | Subchondral bone mineral density |
| SD | Standard deviation |
| STIR | Short tau inversion recovery |
| TASOAC | Tasmanian Older Adult Cohort study |
| TKR | Total knee replacement |
| THR | Total hip replacement |
| US | United States |
| VAS | Visual analog score |
| WOMAC | Western Ontario and McMasters Universities Osteoarthritis Index |
| WORMS | Whole-Organ magnetic resonance imaging score |
| ZA | Zoledronic acid |

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# Abstract

Osteoarthritis (OA) is the most common joint disorder in adults around the world. Knee OA is the most common form of OA in weight-bearing joints and results in deterioration of knee structures and function in older adults for which there is no cost-effective treatment currently available. The natural history of knee OA is highly variable and can involve any part of the joint including the articular cartilage, meniscus, sub-chondral bone and synovium. Use of MRI has revolutionised the understanding of knee OA disease process but there is limited long-term data available in middle-aged adults with early disease changes, as most studies have focused on older adults with established disease. Identifying modifiable risk factors early in life has the potential to prevent or delay the development of knee OA in later life. This thesis aims to investigate the long-term knee structural natural history data in middle-aged adults and subsequent correlations with frequent knee symptoms.

A population-based sample of middle-aged adults (mean age 45(26–61) years; 58% females participated at baseline and approximately 2 and 10 years later. Matched sampling was used to recruit the study participants. Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000. The other half were age and sex matched controls, randomly selected from the population (using electoral rolls) with no history of knee OA in either parent. Cartilage volume, cartilage defects, bone area, bone marrow lesions (BMLs), meniscal tears, meniscal extrusion and effusion were determined using magnetic resonance imaging (MRI). X-ray was used to assess radiographic OA [joint space narrowing (JSN) and osteophytes]. Multiple questionnaires were used to assess pain, function, history of knee joint injury/surgery and physical activity.

The first study examined the cross-sectional association between history of knee injury and knee structural damage assessed on MRI in middle-aged adults from the Offspring study and in a random community based sample of older adults. In middle-aged adults, BML presence, tibial bone area and meniscal extrusion presence were significantly higher in those with knee injury, whereas in older adults, cartilage defect presence, cartilage volume, BML presence and tibial bone area were significantly associated with knee injury. This was the first study to look at the association between history of knee injury and knee joint structural changes assessed on MRI and found that the association between knee injury and MRI-assessed

structural pathology in the knee joint is moderate and appears to be stronger in older adults compared to middle-aged adults.

In the second study, a family history of knee joint replacement due to OA increased the risk of radiographic OA (JSN and osteophytes) and medial tibial cartilage volume loss over 10 years compared to community acquired controls with no family history of OA. Most of these changes were mediated by differences in baseline characteristics of offspring and controls except for increase in medial JSN.

Third study looked at the natural history of BMLs in middle-aged adults and found that the natural history of knee BMLs was unstable. BMLs were common in middle-aged adults at baseline. 24% of these BMLs at baseline increased in size, 55% remained stable and 21% decreased in size or resolved completely over 8 years. Change in BMLs was predicted by BMI and strenuous physical activity. An increase in BML size or a new BML resulted in an increase in pain especially in males and those with a family history of OA.

Fourth study looked at the natural history of meniscal tears. Only 22% of the participants had a meniscal tear at baseline. Over 8 years, 16 % of the participants had an increase in severity of meniscal tears while none improved. Change in meniscal tears shared common risk factors with knee OA and was independently associated with worsening knee pain and structural damage suggesting that meniscal tears are on the knee OA causal pathway and not just a result of mechanical factors.

Fifth study looked at the natural history of cartilage defects. 44% of the participants had at least one cartilage defect at any site at baseline. Most of these defects remained stable, whereas 26% increased and 13% decreased in severity over 10 years. Cartilage defects independently predicted cartilage volume loss in the lateral compartment only. Change in cartilage defects on the other hand was associated with changes in BMI and structural changes/symptoms mostly in the lateral compartment, suggesting a more crucial role of cartilage defects in the development of lateral compartment knee OA.

Sixth study examined the correlation between changes in structural abnormalities assessed on MRI and change in radiographic OA over 10 years. Change in JSN was correlated with change in meniscal tears and, to a lesser extent, with meniscal extrusion and cartilage defects. In this sample, change in JSN was a composite measure that did not reflect cartilage volume

loss prompting the review of the use of JSN as an outcome measure in chondro-protective drug trials.

In conclusion, this series of related studies detail the natural history of knee structural progression in middle-aged adults. Structural changes such as BMLs and cartilage defects have the potential of reversibility in early disease and should be targeted in disease modifying clinical trials. Meniscal tears and BMLs should be targeted in symptom modifying clinical trials especially in those with a family history of OA. Lastly findings from this thesis suggest that the use of JSN as an outcome measure in chondro-protective trial should be reviewed.

# CHAPTER ONE

## Literature Review

## 1.1 Osteoarthritis

Osteoarthritis (OA) is the most common joint disorder, and there is evidence that a majority of individuals over the age of 65 have radiographic and/or clinical evidence of OA [1]. It is a chronic joint disease and commonly involves weight-bearing joints such as the knees, hips, or spine, with hands and neck also being frequently affected sites [2].

Early investigators tended to regard OA as an isolated degenerative disease that resulted from wear and tear, and was an inevitable consequence of aging [3]. Over the past decade there has been a significant shift in the conceptualization of OA etiology and pathogenesis. OA is now considered as the end-point of a complex series of structural changes that result from a series systemic risk factors over many years [4-8]. The old-fashioned wear and tear model has been rejected in favour of a newer and more nuanced inflammatory/molecular model [9, 10]. The synovial joint is now conceptualized as an organ, and OA represents failure of that organ [8]. At a molecular level, the disease occurs when the dynamic equilibrium between the breakdown and repair of the synovial joint tissues is overwhelmed [11].

## 1.2 Knee OA

The knee joint is the most commonly affected weight bearing joint by OA [4, 12]. Nearly one in two older adults are affected by knee OA by the age of 85 [12]. The knee joint is also the site most affected by pain in older adults and most of this is attributed to OA in this age group [12]. Despite the high disease burden, there are currently no registered disease-modifying knee OA drugs available. Therefore, there is an urgent need for research to better understand the disease process and develop cost-effective approaches to prevent or slow down the progression of the disease.

The research conducted in this thesis focuses on knee OA and unless otherwise stated the remainder of the literature review will discuss OA at this site.

### 1.2.1 Burden of disease

As the most common form of joint disease, OA is associated with an extremely high economic burden. This burden is largely attributable to the effects of disability, comorbid disease, and the expense of treatment. Although typically associated with less severe effects on quality of life and per capita expenditures than rheumatoid arthritis [13], OA is nevertheless a more costly disease in economic terms because of its far higher prevalence and lack of cost-effective conservative treatment options available to the patients [14-16]. The global prevalence of radiographically confirmed symptomatic knee and hip OA in 2010 was estimated to be 3.8% and 0.85%, respectively [17]. OA ranked 13th in the top 25 causes of global years lived with disability and the 4th leading cause that showed an increase in the years lived with disability from 1990 to 2013 [13].

1.9 million (or one in 12) Australians suffer from OA costing the health system $3.75 billion and the economy around $22 billion annually [18]. The burden of OA is expected to increase exponentially in coming decades due to an ageing and increasingly obese population, with prevalence expected to reach three million Australians by 2032 [18]. 76.7% of the expenditure on OA is due to admitted patient costs mainly attributed to knee and hip arthroplasties [14]. In 2012-13 there were 103,763 hospitalisations with a principal diagnosis of OA, an increase from 347 hospitalisations per 100,000 population in 2002-03 to 453 per 100,000 population in 2012-13 [14]. Over 85,000 knee and hip replacement procedures (majority due to OA) were performed in Australian hospitals during 2012, each costing an average of $15,000–$31,900 [14]. The number of joint replacements being performed is increasing at a rate of 10% per annum and by 2018, it is expected that the number of joint replacements will be double the number performed in 2012 [14].

While the mortality rate for OA is low, there is also a cost in terms of burden of disease. The pain and disability patients experience can lead to a loss of health and wellbeing, loss of leisure time, and a decreased quality of life. This further contributes to the costs of OA through the loss of production to the economy, increased absenteeism, reduced work capacity and performance, and reduced labour force participation as a result of the related disease morbidity.

### 1.2.2 Applied anatomy of the knee

The knee joint (Figure 1.1) is one of the most complex joints in the human body and is an important joint for locomotion [19]. The knee joint acts as a hinge joint for locomotion resulting in flexion-extension movement of the knee, with only a small degree of axial rotation [20, 21]. During flexion-extension the articular surfaces of the femur roll (and glide) over the tibial and patellar surfaces [21]. The knee joint is therefore conceptualised as two joints—a tibiofemoral and a patellofemoral joint. Functionally the tibiofemoral joint is further divided into the medial and lateral compartments. The medial tibiofemoral compartment is under higher compressive forces due to the way the femur and tibia bones are aligned.

In nearly all circumstances, the knee works in axial compression under the action of gravity. It must therefore reconcile two opposed requirements, namely mobility and stability. This problem is resolved by an ingenious arrangement of soft tissue structures in and around the knee joint [22]. The knee joint is encapsulated by the tendons of the leg muscles, including the patellar tendon, which make the joint movement possible and provides dynamic stability [22]. Anterior cruciate ligament (ACL), posterior cruciate ligament (PCL) and collateral ligaments stabilise the femur and tibia within the knee joint [22]. Articular surfaces of all the

bones are covered by fibrocartilage that help in reducing friction and wear-and-tear on the surfaces of the underlying bones during movement [21]. There are two menisci in the space between the femoral and tibial condyles [21, 23]. These are crescent-shaped lamellae, each with an anterior and a posterior horn, and are triangular in cross section. Menisci aid in load transmission between the femur and tibia bones, act as shock absorbers under compressive forces and protect the articular cartilage from wear-and-tear [24]. Physiological synovial fluid/effusion lubricates all these structures to decrease friction during movement as well [25].

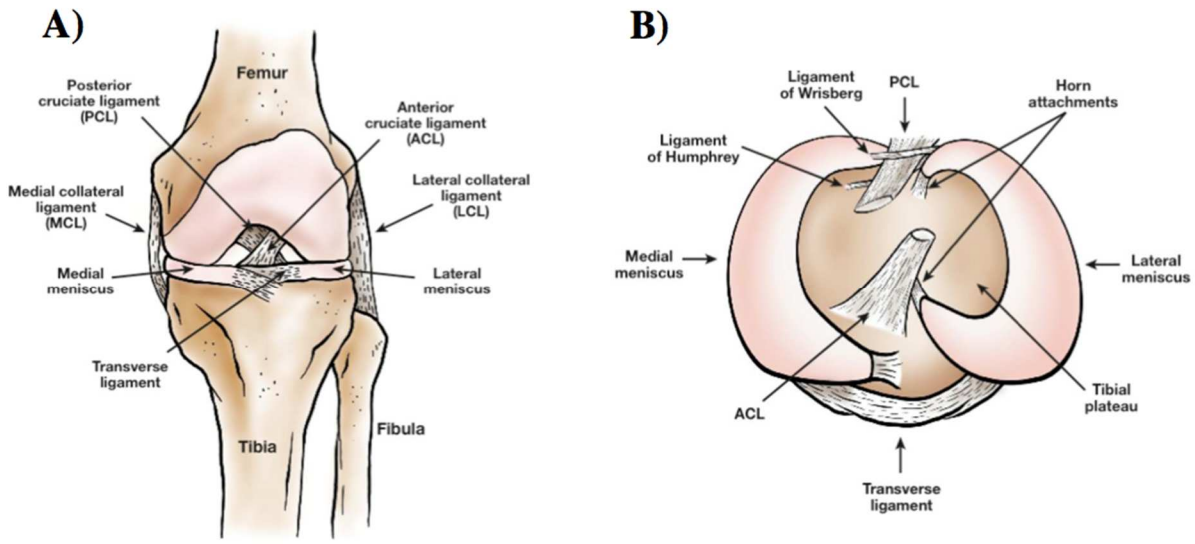


**Figure 1.1.** Knee joint anatomy. **A)** Anterior view **B)** superior view of the tibial plateau (Reproduced with permission from Markis, E. A. *et al*. [26])

### 1.2.3 Knee OA pathophysiology

The natural history of osteoarthritis of the knee is highly variable, with the disease improving in some patients, remaining stable in others, and gradually worsening in others [11]. Traditionally knee OA was regarded as an isolated disease that resulted from articular cartilage volume loss due to age related degenerative process [27]. However advancements in imaging modalities [28, 29] and molecular analyses [30] over the last decade have shown that knee OA is an active process, which can involve any part of the joint. The structural alterations that form the OA disease process are markedly collinear [31], that is, as hyaline articular cartilage becomes morphologically abnormal, other structural processes occur including changes to the meniscus, bone marrow, sub-chondral bone, synovial lining, ligaments and peri-articular muscles.

### 1.2.4 Symptoms

OA represents one of the most frequently occurring painful conditions [12, 17, 32]. Pain is the most common symptom in OA and the usual reason for seeking medical advice [32]. According to the National Health Survey 2011-12 [33], people aged 18 and over with osteoarthritis were 3.5 times more likely to report very severe pain (4.9%) compared with those without OA (1.4%). Other signs and symptoms of the disease include joint stiffness, tenderness, inflammation, crepitus, instability, and muscle weakness [34-36]. These symptoms are initially felt during and after activity, but as the disease progresses it may occur with minimal movement or even during rest [36]. Knee pain is associated with a considerable reduction in functional ability [12, 35], which in turn strongly predicts future disability and dependency [36].

Approximately 25 percent of persons 55 years of age or older have had knee pain on most days in a month in the past year, and about half of them have radiographic evidence of knee OA, a group considered to have symptomatic OA [33, 36]. The prevalence of symptomatic knee OA and knee pain has increased substantially over the past 20 years, independent of age and obesity [34]. OA is also the most common cause of chronic pain especially in older adults [32]. This suggests that as the Australian population ages, the prevalence of OA-

induced chronic pain will increase.

The determinants of pain and structural damage in OA are not well understood but are believed to involve multiple interactive pathways [37]. OA pain is a mixed phenomenon where nociceptive [38] and neuropathic [36, 39] mechanisms are involved in both the local and central levels. OA pain perception is influenced by multiple environmental, psychological, or constitutional factors, and OA pain intensity is not just determined by the structural damage in the synovial joint [37]. Subjects with the same degree of structural damage experience widely different levels of pain, a phenomenon that is poorly understood. Whilst radiographic evidence of joint damage predisposes to joint pain, it is clear that the relation of the severity of joint damage to the severity of the pain is not strong [8, 40]. However, using other imaging modalities such as magnetic resonance imaging (MRI), numerous structural alterations have been related to knee pain. It remains unclear, which of these local tissue factors predominate.

Constitutional factors that can predispose to symptoms including self-efficacy, pain catastrophizing and the social context of the disease (social support, pain communication) are all important considerations in understanding the pain experience [41]. The limitations imposed by OA can be detrimental to a person's self-esteem and self-image and can lead to negative emotional states, anxiety, depression and feelings of helplessness that can in turn exacerbate the perception of symptoms [42]. There is also evidence that genetic factors may also influence the pain perception pathways. Candidate genes have been identified which could alter the processing of nociceptive pain associated with OA [43].

### 1.2.5 Risk factors

OA is a multifactorial disease and the development of the disease is dependent on interactions between several factors. This process may be considered the product of interplay between systemic and local factors [44]. Risk factors vary for different joints, for different stages of disease, and for the development versus the progression of the disease.

Age remains one of the strongest risk factors for the development of knee OA [45]. Knee OA can occur at any age but the relationship between age and the development of knee OA is

non-linear. Population based studies have indicated a sharp increase in the incidence of knee OA between the ages of 50 and 75 years [46] and a levelling off or a decline after the age of 80 years [47].

Obesity or being overweight is probably the most important risk factor for the development and progression of not only knee OA but also at other sites such as hands and hip [45]. Mechanical forces exerted on the knee joint are a significant cause of OA and body mass index (BMI) is one of the most important modifiable risk factors [48, 49]. Relationship between obesity and the development of knee OA is mainly linear [48]. Obesity alone or in patients with metabolic syndrome increases the risk of radiographic knee OA [50, 51]. One study found that increasing from normal to overweight during adult life might give a slightly higher risk of developing knee OA than being constantly overweight during adult life [49]. Another study found that among women at an elevated risk of OA due to high BMI, weight loss decreased this risk substantially [52]. A meta-analysis showed that over-weight people had higher odds (odds ratio (OR) 1.98 (95% CI 1.57-2.20) for developing knee OA and the risk increased further in obese people (OR=2.66 (95% CI 2.15-3.28)) [49]. Moreover an estimated 17.3-24.6% of new cases of knee pain are related to being overweight or obese [45]. Another study estimated that 69% of the knee arthroplasties are attributed to obesity [51].

Females are at a higher risk of developing knee OA (OR=1.68 (95% CI 1.37-2.07)) [45]. Prevalence of knee OA is roughly the same in males and females in younger adults but the prevalence increases in females after menopause[53]. Twice as many females suffer from the disease compared to males between the ages of 50-80 years [54]. These findings suggest a role of sex hormones but the evidence supporting the role of specific sex hormones thus far has been inconsistent [45].

History of joint injury is widely accepted as a contributory factor in the development of knee OA. Major trauma to the knee has the potential for damage to any of the knee structures that are important for joint homeostasis. Several epidemiological studies have shown this association using radiography. In a prospective cohort study, Wilder *et al.* [55] showed that individuals with a history of knee injury were 7.4 times more likely to develop knee ROA than individuals who did not have a history of knee injury. A recent meta-analysis showed

that history of knee injury was consistently associated with higher odds of developing knee OA (OR= 2.83 (95% CI 1.91-4.19)) [45]. The same study also estimated that 5.1% of new knee pain/OA patients could be attributed to a previous knee joint injury [51].

Systemic predisposition is also a potent risk factor for knee OA. Several studies have shown that OA is often generalized and affects multiple joints. In a post-mortem bone study, Rogers *et al.* [56] confirmed the hypothesis that OA is caused primarily by a systemic predisposition. Hand OA, usually diagnosed clinically by the presence of Heberden's nodes, increases the odds for the development of the knee OA (OR=1.30 (95% CI 0.90-1.87)) [45].

Other common risk factors mentioned in the literature include occupational risk factors, physical activity and genetic factors. Occupational risk factors include work involving kneeling/bending [57-59] and heavy lifting [58-60]. Similarly farmers and construction workers are also at a higher risk of developing knee OA [61]. Evidence for physical activity is rather inconsistent. Intense physical activities such as long-distance running have been shown to increase the risk of developing knee OA [62-64]. Similarly Dore *et al.* [65] showed that >10,000 steps/day are associated with worsening knee structures. However, Felson *et al.* [66] and Øiestad *et al.* [67] did not see any association between objectively assessed physical activity and progressive knee structural damage. There is strong evidence that genetic factors play an important role in the development of OA of the hands and the spine [68, 69]. The evidence is rather inconsistent for knee OA [68-72] and it has proven difficult to isolate candidate genes [73].

## 1.2.6 Diagnosis

OA is diagnosed using a combination of clinical examination and imaging [74].

### 1.2.6.1 Clinical criteria

Knee OA is defined clinically using frequent knee symptoms. The American College of Rheumatology (ACR) definition for symptomatic OA is most commonly used and defines OA as “pain, aching, or stiffness in or around the knee on most days” for at least one month

during the past 12 months [74]. This definition has been validated by several epidemiological studies [75, 76]. This definition is however simplistic and does not take into account the severity of pain. Several pain scores, such as the Visual Analog Score (VAS), the Knee injury and Osteoarthritis Outcome Score (KOOS) [77] and the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) [78], have been developed for research purpose's and take into account the severity of knee pain and longitudinal changes in the severity of the symptoms.

#### 1.2.6.2 Imaging

Imaging studies have provided many insights, however much remains unknown and uncertain. Imaging developments in OA are an important rate-limiting step to further therapeutic development.

Radiographs remain the gold standard for diagnosing OA. Radiography enables the detection of OA-associated bony features such as osteophytes, subchondral sclerosis, and cysts [79]. Radiographs can also determine joint space narrowing (JSN) [79] that is traditionally thought to result from cartilage volume loss but may also reflect changes in meniscal integrity [31]. Although radiographs cannot directly assess any of the intra-articular soft tissue structures, radiography is still the only method approved by Food and Drug Administration (FDA) for monitoring disease progression in the Disease Modifying Osteoarthritis Drug (DMOAD) Trials [80].

The severity of radiographic OA can be assessed with semi-quantitative scoring systems. The Kellgren and Lawrence (KL) [81] grading system (Table 1.1) was the earliest proposed and one of most widely used scoring system. KL grading system defines radiographic OA based on the presence of a definite osteophyte (grade 2). However, KL grading has its limitations; in particular, KL grade 3 includes all degrees of definite JSN, regardless of the extent. Secondly it places too much emphasis on osteophytes.

The research conducted in this thesis used the atlas from the Osteoarthritis Research Society International (OARSI) (Table 1.2), which was first published in 1995, by Altman *et al.* [82, 83]. The OARSI atlas provides grades for specific features of OA rather than global scores

like the KL scheme. The atlas grades tibiofemoral JSN (Figure 1.2) and osteophytes (Figure 1.3) (on a 0-3 grade where 0=absent and 3=severe) separately for each compartment of the knee (medial tibiofemoral, lateral tibiofemoral, and patellofemoral). The OARSI atlas provides clinicians and researchers with a standardised semi-quantitative methodology for radiographic features and has been validated in both cross-sectional and longitudinal studies.

**Table 1.1.** Kellgren and Lawrence (K/L) grading system

| Grades | Description |
|---|---|
| Grade 0: No osteoarthritis | No osteoarthritis |
| Grade 1: Doubtful | Doubtful narrowing of joint space and possible osteophytic lipping |
| Grade 2: Mild | Definite osteophytes and possible narrowing of joint space |
| Grade 3: Moderate | Multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends |
| Grade 4: Severe | Large osteophyte, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends |

**Table 1.2.** Individual radiographic features measured by the OARSI atlas for tibiofemoral osteoarthritis

| Radiographic Features | Score |
|---|---|
| **Marginal osteophytes** | |
| Medial femoral condyle | 0-3 |
| Medial tibial plateau | 0-3 |
| Lateral femoral condyle | 0-3 |
| Lateral tibial plateau | 0-3 |
| **Joint space narrowing** | |
| Medial compartment | 0-3 |
| Lateral compartment | 0-3 |
| **Other** | |
| Medial tibial attrition | Absent/present |
| Medial tibial sclerosis | Absent/present |
| Lateral femoral sclerosis | Absent/present |

OARSI: Osteoarthritis Research Society International

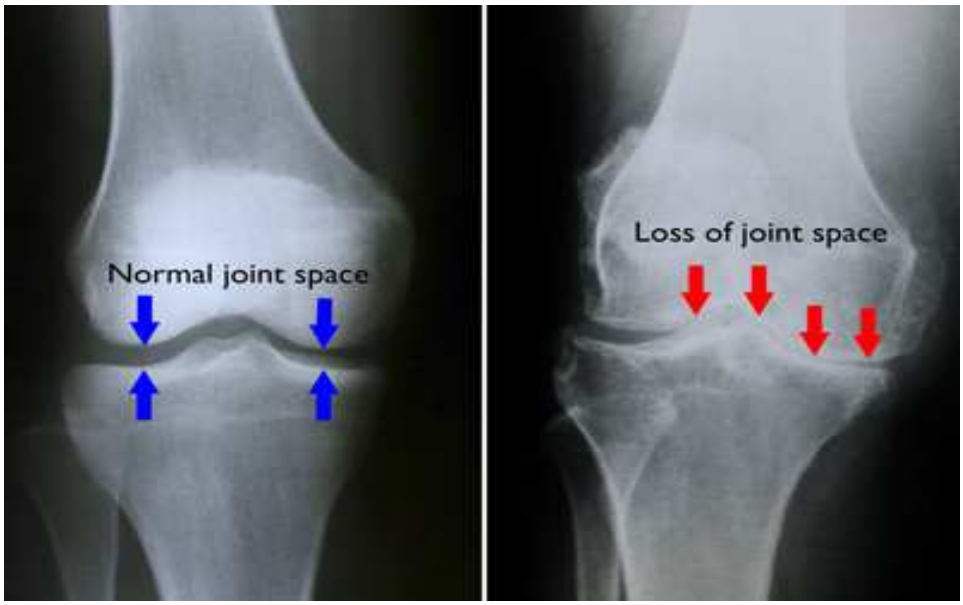


**Figure 1.2.** Radiographic joint space narrowing

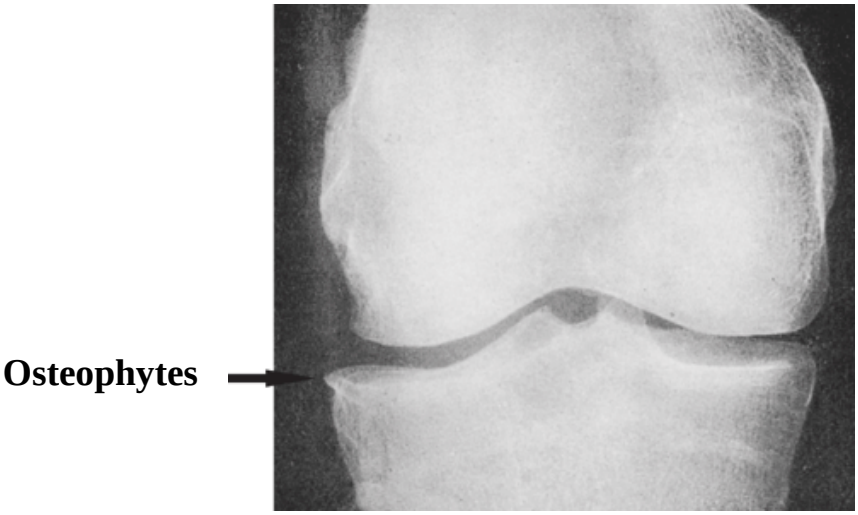


**Figure 1.3.** Radiographic osteophytes

### 1.2.7 Radiography versus MRI

Radiographs are still the standard modality to diagnose OA and to monitor disease progression in clinical trials [79]. Radiographs do have certain advantages [8, 79]. Firstly, radiographs are cheaper compared to other imaging modalities and readily available. Secondly radiographic scoring systems are standardised, which makes them easier to implement in both clinical and large multicentre research settings.

Radiographs do have certain limitations that have seen the continued use of radiographs as an outcome measure in OA research criticised. Radiographs have a low resolution and cannot directly visualise the soft tissue structures that make up the knee joint such as cartilage, meniscus and ligaments. Subject positioning and changes in the radio-anatomic alignment of the knee joint in serial examinations influence the reproducibility of radiographs [31]. Radiography is also insensitive to early disease changes. Approximately 10% of the knee articular cartilage is already lost before we observe any changes on the radiographs [84]. Similarly radiographs are also insensitive to small changes overtime [85]. Longitudinal studies require a long follow-up period before we can observe any appreciable changes on radiographs making the studies more time consuming and expensive. Lastly several studies have shown that radiographic features such as JSN and osteophytes do not correlate well with clinical symptoms. In population studies, there is a significant discordance between radiographically diagnosed OA and knee pain and vice versa [8, 40, 86-88]. Although radiographic evidence of joint damage predisposes to joint pain, it is clear that the relation of the severity of joint damage to the severity of the pain is not strong. In a systematic review, Bedson *et al.* [87] reported that the proportion of knee pain found to have ROA ranged from 15–76% and in those with ROA the proportion with pain ranged from 15–81%.

MRI has proven to be an important alternative imaging tool in OA research and has revolutionised the understanding of OA pathology. The cross-sectional image display, spatial resolution, and tissue contrast of MRI enables whole organ assessment of the knee joint [28]. MRI is ideally suited for imaging arthritic joints, as is it free of ionizing radiation and has the ability to acquire morphological and biochemical data [28]. Advances in MRI technology have improved its ability to detect bone marrow lesions, joint fluid changes, ligamentous and

meniscal damage, osteophyte formation, cartilage morphology, as well as macromolecular changes, which often precede morphological changes [8].

As mentioned earlier, there is a significant discordance between radiographically diagnosed OA and knee symptoms. Radiographic disease predisposes to knee symptoms but the extent of joint damage does not correlate well with the severity of knee pain [8]. Several population-based studies using MRI have described associations between knee pain and knee structures such cartilage defects [89, 90], BMLs [91-93], meniscal damage [75, 94] and effusion/synovitis [7, 95]. Recent evidence has clearly shown that most of the soft tissue changes in the knee joint OA causal pathway are collinear [31]. However it is not clear which of these structures predominantly result in knee pain as most of the earlier studies did not account for all the soft tissues that can result in symptoms. For example cartilage is an aneural and an avascular structure and theoretically cartilage damage should not result in symptoms unless the subchondral bone is denuded. However, several studies have shown an association between cartilage defects/thickness loss and knee symptoms [89, 90]. These positive associations are most likely due to the fact that these studies did not account for global knee structural changes [96].

To develop new treatments to prevent the progression of OA, we need to understand what subtle changes occur at different stages of the disease. Extensive use of MRI to study knee OA pathophysiology has provided us with great insight into different soft tissues that can be targeted. Structural abnormalities can be assessed either semi-quantitatively or quantitatively. Several semi-quantitative scores such as Whole-Organ Magnetic Resonance Imaging Score (WORMS) [97], Knee Osteoarthritis Scoring System (KOSS) [98] and Boston–Leeds Osteoarthritis Knee Score (BLOKS) [92] have been proposed and have generally shown good reliability and specificity. However, as with any ordinal scale, these semi-quantitative scores lack sensitivity to change over time. Large-scale population based studies using MRI are expensive and require long follow-up periods to have adequate sensitivity to detect change in knee structures using ordinal scales. Most of the earlier studies using MRI to assess knee OA were either cross-sectional or had short follow-up periods, which makes semi-quantitative scales less sensitive to detect longitudinal progression.

Several manual, semi-automated and automated image processing softwares have been developed to quantitatively assess knee structural abnormalities. Quantitative assessment of the knee articular cartilage is particularly important, as articular cartilage loss is often cited as the structural hallmark of OA progression. Commonly used sequences for morphological MR imaging include original and fast or three-dimensional (3D) variations of spin-echo (SE) and gradient-recalled echo (GRE) and 3D dual-echo steady state (3D DESS). Cartilage boundaries in different knee compartments (tibial, femoral and patellar) are usually segmented on a slice-by-slice basis and then extrapolated to assess cartilage volume. The measurement of cartilage volume from MRI has been shown to correlate well with the ex-vivo assessments of cartilage volume [99, 100]. Quantitative assessment techniques for other structural abnormalities such BML area, bone area, meniscal extrusion and knee effusion area/volume have also shown to be reproducible and sensitive to change over time.

Currently no DMOADs are available to slow the progression or reverse structural damage that results from OA. The biggest obstacle in developing an effective treatment modality is the lack of suitable imaging modalities to monitor disease progression and serve as an end-point in DMOAD trials. An ideal imaging modality should be able to visualize global knee structural abnormalities, should be reproducible, should correlate well with symptoms, should be able to detect earlier structural abnormalities before changes become irreversible and should be sensitive to subtle changes over a short period of time. Despite the obvious limitations, radiographs remain the current gold standard to diagnose knee OA and is the only modality approved by Food and Drug Administration (FDA) to show efficacy of disease modifying OA drugs in phase 3 clinical trials [79].

MRI has become a key imaging tool for OA research because of its ability to visualize disease in structures not imaged by radiography, ability to monitor multiple tissue changes simultaneously over several time points and the ability to detect physiologic changes within joint tissues (eg, cartilage and menisci) before morphologic changes become apparent. Yet there are several reasons why MRI is not the gold standard for diagnosing knee OA and monitoring disease progression. Firstly there is a lack of clarity about the diagnostic performance of different soft tissue abnormalities found on MRI scans as there is a lack of long term studies looking at the predictive value of these early structural changes [101]. Secondly there is a lot of contradictory data available [101] looking at the association

between structural changes and symptoms, as most of the earlier studies did not account for global knee structural abnormalities. Thirdly there is a lack of standardisation due to the absence of a MRI structural definition of OA [101]. Using a modified Delphi approach, a panel of experts in the field have developed 11 propositions for a definition of knee OA on MRI [101]. The goal of this exercise was to develop definitions of knee OA that can be more formally tested in relation to their diagnostic performance in long-term studies. Lastly and most importantly the majority of long-term studies have thus far focused on older aged populations with established symptomatic disease. There is little long-term MRI data available for knee structural changes especially in early disease.

### 1.2.8 Why study middle-aged adults?

Knee OA is a disease that mostly affects older adults and it made sense for earlier studies to focus on older populations with advanced symptomatic disease. However once the disease is established, there is little potential of any reversibility. It is important to detect early disease changes in middle-aged groups with little or no radiographic changes and symptoms. This would firstly allow us to study the natural history of soft tissue abnormalities and understand how knee OA evolves. Studying the natural history of knee structural changes can help us identify people who are fast-progressors, making recruitment for clinical trials more efficient and treatments possibly more effective. Furthermore, studying middle-aged populations can help us identify pathological abnormalities that trigger OA development and identify factors that can possibly prevent, delay or slow down OA progression. We can also possibly identify tissues with potential of regeneration before irreversible damage sets in. Targeting the right populations and early structural abnormalities is imperative for the success of future DMOAD trials.

## 1.3 Offspring Study

The Offspring study [102, 103] is a longitudinal controlled population-based study of middle-aged adults (more detailed description of the Offspring study is provided in the Methods

section). The Offspring study began in Southern Tasmania in June 2000. Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA and the other half were age and sex matched controls without a family history of knee OA. First follow-up was after two years and the second follow-up was after ten years (this thesis mainly used the ten-year follow-up data). The Offspring study was one of the first large scale population based longitudinal studies to use MRI data to investigate knee OA, the first major MRI based knee OA study in middle aged adults and currently the longest follow-up knee OA study with MRI data.

### 1.3.1 Evidence from earlier phases of Offspring study

Offspring/control differences

Cross-sectional baseline data showed that compared to controls, offspring were significantly heavier, had a higher prevalence of knee pain, weaker lower limb muscles, a larger tibial bone area and a higher prevalence of cartilage defects [104]. There was no significant difference between the two groups for the prevalence of ROA and mean cartilage volume [104]. Similarly cartilage volume, muscle strength, bone area and BMLs showed high heritability in sib-pair analysis [70].

Pain/symptoms

Cross-sectional data from the baseline visit of the Offspring study showed that knee pain was fairly common in middle-aged adults with a prevalence of 35% [105]. However the severity of knee pain was low [105]. Knee pain was independently associated with non-full thickness chondral defects (particularly femoral and patellar), osteophytes, urinary C-terminal cross-linking telopeptide of type II collagen (CTX-II) and obesity [105]. Separate studies from the first follow-up of the Offspring study showed that the prevalence of both BMLs [106] and meniscal tears [94] were significantly associated with knee pain, however the magnitude of the associations remained low.

Cartilage defects and cartilage volume loss

Cartilage defects were very common with a prevalence of 44% [89]. Presence of cartilage defects was associated with low cartilage volume (in a dose response manner) and with urinary CTX-II [89]. Another important finding was that cartilage volume loss started about the age of 40 in most people and the rate of loss was about 2% per annum and increased with age, consistent with the natural history OA [107]. Cartilage defects at baseline also independently predicted cartilage volume loss over 2 years [108]. Natural history of cartilage defects was quite variable [89]. Approximately one-third of the cartilage defects increased in severity but interestingly a similar number decreased in severity or completely resolved over 2 years. These findings suggest that OA structural damage is not irreversible especially in younger adults.

BMLs

A cross-sectional study from first follow-up of the Offspring study was the first population-based study to examine the risk factors for the development of BMLs [106]. BMLs were fairly common in middle aged adults (24% in the medial tibiofemoral compartment and 14% in the lateral tibiofemoral compartment). Besides genetic factors, presence of BMLs was positively associated male gender, BMI, cartilage defects and ROA.

Meniscus

Meniscal tears are generally thought to result from mechanical factors such as knee injury/surgery. A cross-sectional study [94] from the Offspring study was one of the earliest studies to suggest that meniscal tears share common risk factors with OA. Meniscal tears were not only associated with symptoms but also with cartilage defects, cartilage volume and ROA. In summary, earlier visits of the Offspring study provided valuable cross-sectional and short term MRI data. However long-term data was required to better understand the natural history of knee structural changes, correlation between structural changes and symptoms and validate MRI changes against long-term radiographic changes.

## 1.4 Summary

About 8% of Australians are affected by OA. By 2050, it is projected that the prevalence of OA will be 11% of the population. OA is a leading source of health expenditure on arthritis, accounting just under half of total allocated expenditure on arthritis in 2007. There was a 54% rise in total knee replacements for OA from 2002-03 to 2011-12. There are no disease-modifying treatments available for OA. There is an urgent need for identifying modifiable risk factors for this disease and for understanding early structural changes. Identifying these factors before knee structural damage becomes irreversible can delay or may even prevent the development of knee OA later in life. The following Chapters describe long-term knee structural natural history data in middle-aged adults and the correlation with frequent knee symptoms. Ten year follow-up data from the Offspring study was used to explore these questions. The specific research questions that directed this work are described in the following Chapter.

# CHAPTER TWO

## Research Questions

## 2.1 Research Questions

A population-based sample of middle-aged adults, with an offspring-control design, was examined at baseline and approximately 2 and 10 years later:

1. What the cross-sectional association between history of knee injury and knee structural damage assessed on MRI in middle-aged adults from the Offspring study and how does that compare to a random community based sample of older adults.
2. Does a family history of knee joint replacement due to OA increase the risk of radiographic OA progression and cartilage volume loss over 10 years?
3. What is the long-term natural history of BMLs in middle-aged adults and how are these changes associated with symptoms and other knee structural changes?
4. What is the natural history of meniscal tears in middle-aged adults and how are these changes associated with symptoms and structural changes?
5. What is the long-term natural history of cartilage defects, do cartilage defects predict cartilage volume loss and how changes in cartilage defects are associated with changes in symptoms and structure?
6. How do changes on MRI correlate with changes in radiographs and whether radiographic JSN should be used as an end-point in chondro=protective drug trials?

## 2.2 Key Hypothesis

1. Family history of OA influences structural progression and symptoms associated with knee OA
2. Studying the long-term natural history in middle-aged will help identify reversible structural changes which can potentially be targeted in clinical drug trials.

# CHAPTER THREE

## Methodology

## 3.1 Prelude

This thesis arose from analyses of the Offspring study population, and a number of outcome factors, study factors, and covariates have been utilised. This chapter describes the Offspring study population and its design, as well as the protocols for measurement of factors that are common to multiple chapters in this thesis. Additional factors, which are unique to each chapter, are described in more detail within the methodology section of each of the subsequent chapters.

It should be noted that the following chapters are presented in the form in which they were submitted to, or accepted by, peer-reviewed journals for publication. Thus, throughout these chapters there are some differences in the description of methods, analyses, results, and interpretations, due chiefly to requests from journal reviewers.

## 3.2 Study population and design

The work in this thesis was conducted as part of the Offspring study, a population-based study with an Offspring-control design, aimed at identifying the environmental, genetic, and biochemical factors associated with the development and progression of knee osteoarthritis (OA). The Offspring study began in Southern Tasmania (primarily in the city of Hobart) in June 2000. Matched sampling was used to recruit the study participants (mean age 45(26–61) years; 58% females) [102]. Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiographs when possible. The other half were age and sex matched controls, randomly selected from the population (using electoral rolls) with no history of knee OA in either parent. Electoral rolls represent the most complete population information available in Australia because voting in federal and state elections is compulsory. This thesis includes data from visit-1 (2000-01), visit-2 (2002-03) and visit-3 (2010-11) of the study.

Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). Participants were also excluded if

they had undergone a knee replacement surgery or did so after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

Figure 3.1 provides an overview of participant recruitment and withdrawal during the study period. Offspring study started with 372 participants (Offspring=186 and Controls=186) in year 2000. 326 (88%) participants (Offspring= 162 and Controls= 164) were followed up after approximately 2 years, whereas 220 (59%) participants (Offspring= 115 and Controls= 105) were followed up after approximately 10 years.

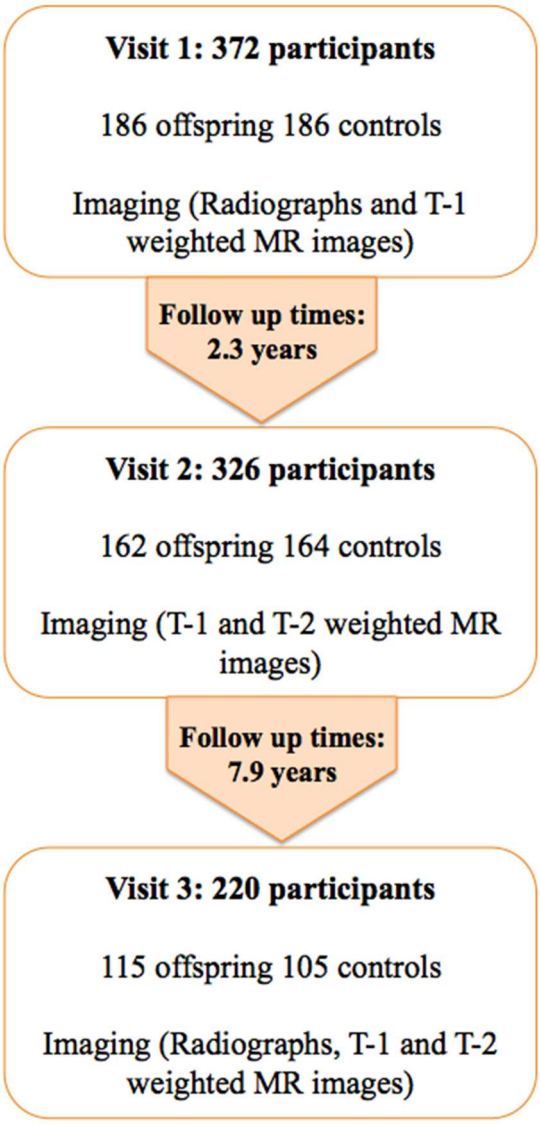


**Figure 3.1.** Flow chart Offspring study

Table 3.1 summarises the baseline characteristics of those participants who completed the follow-up (n=220) and those which did not (n=152). There was no significant difference in age, sex, BMI, proportion of Offspring (%) and prevalence of ROA and knee pain between the two groups.

The sample size used in the following chapters of this thesis varies depending on the available data for each of the research questions.

**Table 3.1:** Baseline characteristics of the participants who were followed-up and who were lost to follow up

| Characteristic | Follow-up (n = 220) | Loss Follow-up (n = 152) | P-value |
|---|---|---|---|
| Age (years) | 45.3 ± 6.7 | 45.1 ± 7.2 | 0.806 |
| Female (%) | 58 | 59 | 0.749* |
| BMI (kg/m$^2$) | 27.2 ± 4.9 | 26.8 ± 4.3 | 0.499 |
| Offspring (%) | 52 | 47 | 0.891* |
| Radiographic OA (%) | 18 | 15 | 0.486* |
| Knee pain present (%) | 33 | 34 | 0.917* |

Mean ± standard deviation except for percentages; *Determined by Chi square test, others by t-test

## 3.3 Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$).

## 3.4 Leg strength

Muscle strength was measured by dynamometry at the lower limb (involving both legs simultaneously) at all three visits. This primarily involves the hip flexors and knee extensors. The participants were instructed in each technique prior to testing, and each measure was performed twice. The repeatability estimate (Cronbach's alpha) was 0.9 [70]. The device was calibrated by suspending known weights at regular intervals.

## 3.5 Knee joint injury and surgery

History of knee joint injury and surgery were assessed using a self-administered questionnaire which included the following questions and was identical in both cohorts:

"Have you ever had a previous knee injury which resulted in non-weight bearing treatment for 24 hours or more?"

"If yes, then which knee?"

"Please provide further details about the injury"

"Have you ever had a knee surgery?"

"If yes, then which knee?"

"Please provide further details about the surgery"

## 3.6 Knee pain

Knee pain was assessed at visit-1 using an interviewer-administered questionnaire as described previously [102]. All the participants were asked the following question:

Have you had knee pain for more than 24 hours in the last 12 months or daily pain on greater than 30 days in the last year?

Knee pain was assessed by self-administered questionnaire using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [93] at visits 2 and 3. Five categories of pain (walking on flat surface, going up or down stairs, at night, sitting or lying, and standing upright) were assessed separately with a 10-point scale from 0 (no pain) to 10 (most severe pain). Each category was summed to create a total pain score (range 0 to 50). Furthermore, the five categories were clinically categorized into weight-bearing pain (including walking on flat surface, going up or down stairs and standing) and non-weight-bearing pain (including pain at night and sitting or lying).

## 3.7 Magnetic Resonance Imaging

MRI of the right knee was acquired at all three visits with a 1.5T whole-body magnetic resonance unit (Picker, Cleveland, OH, USA) using a commercial transmit/receive extremity coil [89, 104, 108]. The following image sequences were used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 msec, echo time 12 msec, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an interslice-gap (at all three visits); and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256×256 matrix, slice thickness of 4 mm with an interslice gap of 0.5–1.0 mm (at visit 2 and 3).

The same scanner (same model and machine) was used at all the three visits for both T1-weighted fat-suppressed and T2-weighted fat saturation images.

### 3.7.1 Cartilage volume

Tibial and patellar cartilage volume was assessed at all three time points, by a trained observer on T1-weighted MR images, using Osiris (University of Geneva, Geneva, Switzerland) software as previously described [104, 109]. The image data were transferred to the workstation. The volumes of individual cartilage plates (medial tibial, lateral tibial and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 µm and 1.5mm thickness, continuous sections) for the final 3D rendering using Osiris software. The coefficient of variation (CV) for both studies ranged between 2.1–2.2% for intra-observer repeatability [84]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Quebec, Canada), as previously described [110, 111]. First, using a semi-automated image processing (segmentation), the whole cartilage geometry is extracted from MR sagittal range images (Figure 3.2). For each sagittal image in the volume data set, semi-automatic delineation is performed using an active-contour-segmentation technique. These initial contour lines are then automatically adjusted by using a 2D/3D; active-contour process (snake) to more closely fit the cartilage margins with sub-pixel accuracy, as already described [111, 112]. The CV for both studies was approximately 2% for intra-observer and inter-scan repeatability [111, 112].

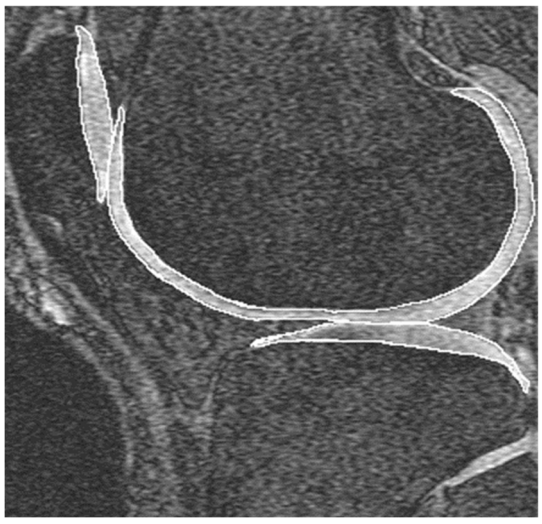

**Figure 3.2.** Cartilage volume segmentation

### 3.7.2 Cartilage defects

Cartilage defects were assessed on T1-weighted gradient echo MR images at all three visits. Cartilage defects were graded at the medial tibial, medial femoral, lateral tibial, lateral femoral and patellar sites on a 0-4 scale (grade-0=normal cartilage; grade-1=focal blistering and intra-cartilaginous low-signal intensity area with an intact surface and bottom; grade-2=irregularities on the surface or bottom and loss of thickness of less than 50%; grade-3=deep ulceration with loss of thickness of more than 50%; grade-4=full-thickness chondral wear with exposure of sub-chondral bone), as previously described [113] (Figure 3.3). A cartilage defect also had to be present in at least two consecutive slices. If multiple defects existed at one site, the highest grade was used. Intra-observer reliability (expressed as intra-class correlation coefficient (ICC)) ranged from 0.89-0.90. Inter-observer reliability was assessed in 50 MR images and yielded an ICC of 0.85-0.90.

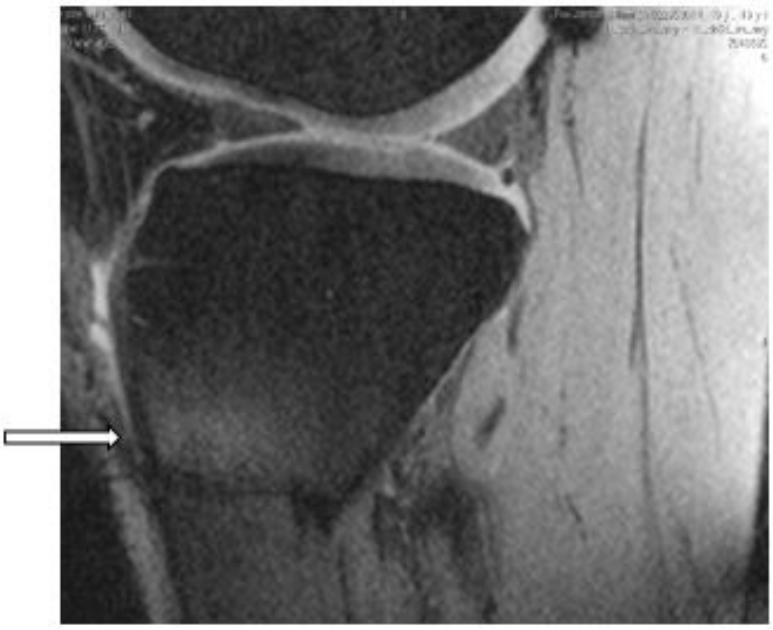

**Figure 3.3.** Grade-2 cartilage defect

### 3.7.3 Bone marrow lesions

Subchondral BMLs were assessed at visit 2 and 3, using Osiris software (University of Geneva, Geneva, Switzerland) and were defined as areas of increased signal adjacent to the

subcortical bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella and inferior patella sites[93] (Figure 3.4). One trained observer scored the BMLs by measuring the maximum area ($cm^2$) of the lesion at both time points. The observer manually selected the MRI slice with the greatest BML size. The BML with the highest score was used if more than one lesion was present at the same site. MRIs at both time points were read paired with the chronological order known to the observer and the observer blinded to clinical status. Intraobserver repeatability was assessed in 40 subjects with at least a two-week interval between the readings. The ICC was 0.97. Participants were given a BML score ($cm^2$) for each of the six sites (medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella and inferior patella sites).

**Figure 3.4.** Bone marrow lesion

## 3.7.4 Meniscal tears

Meniscal tears were assessed by a trained observer (musculoskeletal radiologist with several years of experience) on T2-weighted fat saturated (side by side) MR images at visit-2 and 3 of the study as previously described [110] (Figure 3.5). The proportion of the menisci

affected by a tear was scored separately (0-2 scale; 0=absence of a tear, 1=simple tear of different types: longitudinal, oblique, radial or horizontal, 2=macerated tear signifying loss>50% area of meniscal tissue) at the anterior, middle, and posterior horns. Anterior, middle and posterior scores were summed to create medial and lateral meniscal tear scores. The intra- and inter-observer correlation coefficient (expressed as ICC) ranged from 0.86 to 0.96 [111].

Meniscal tears were initially scored cross-sectionally on T-1 weighted MR images using a different protocol at Visit-2 of the study. More details of the exact protocol are provided in Chapter 4.

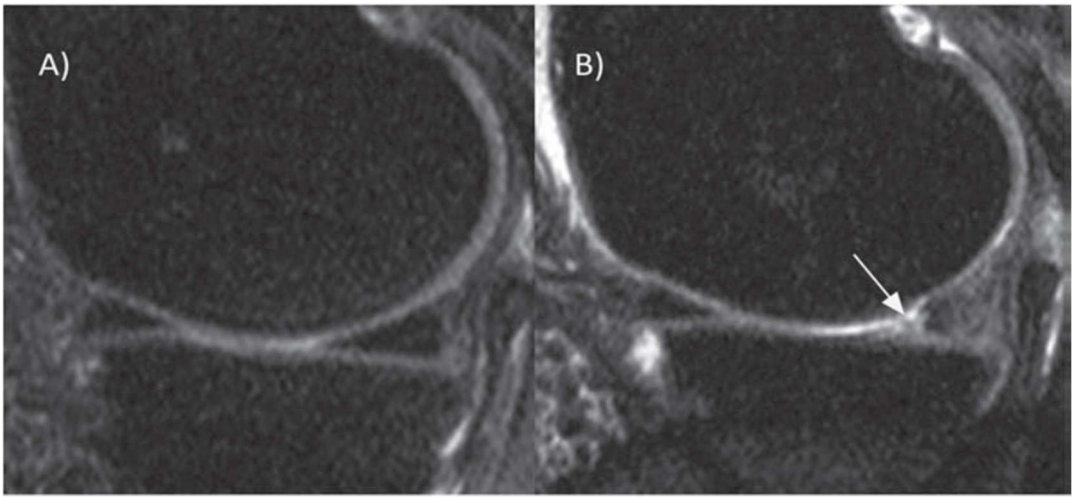


**Figure 3.5. A).** Normal meniscus. **B)** Meniscal tear

## 3.7.5 Meniscal extrusion

The extent of meniscal extrusion on the medial or lateral edges of the tibial femoral joint space, not including the osteophytes, was evaluated at visit-2 and 3 for the anterior, body, and posterior horns of the menisci on T1-weighted gradient echo MR images, as previously described[111]. A score from 0 to 2 was used (0= no extrusion, 1= partial meniscal extrusion, and 2= complete meniscal extrusion with no contact with the joint space). The scores of anterior, body and posterior horns of medial or lateral menisci were summed to create a total meniscal extrusion score for each of the medial and lateral tibiofemoral compartments which

had a possible range from 0 to 6. The intra- and inter-observer correlation coefficient (expressed as ICC) ranged from 0.85 to 0.92 for meniscal extrusion [110].

### 3.7.6 Tibial bone area

Knee tibial plateau bone area was assessed on T1-weighted MR images at visits 1 and 2, and determined by means of image processing on an independent workstation using the software program Osiris (University of Geneva) as previously described [104]. To transform the images from the sagittal plane to the axial plane, the Analyse Software package developed by the Mayo Clinic was employed. Medial and lateral tibial plateau bone area was determined by creating an isotropic volume from the three input images closest to the knee joint (Figure 3.6). The bone area of the medial and lateral tibial plateau was then directly measured from the reformatted axial images. The CV was 2.2–2.6% for intra- observer repeatability[104].

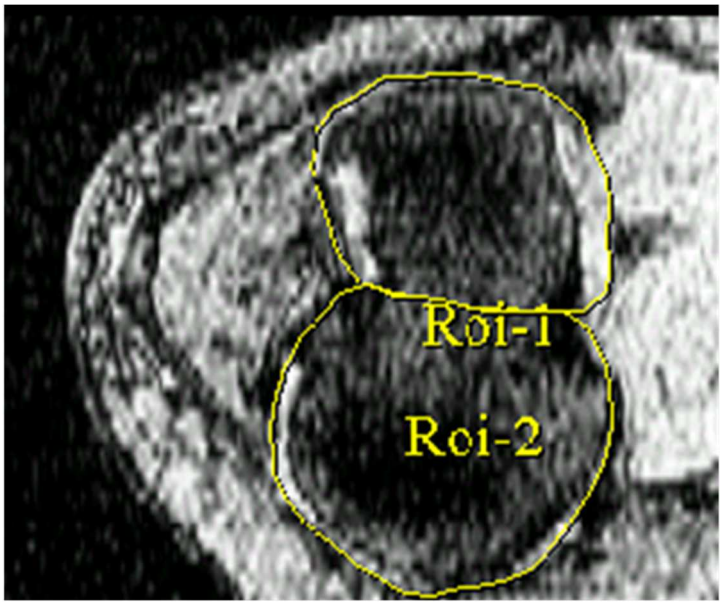


**Figure 3.6.** Medial and lateral tibial bone area

### 3.7.7 Effusion

Effusion was assessed in the supra-patellar pouch on T2-weighted fat saturated MR images at visits 2 and 3 on a 0-3 scale[114]. Grade-0 signified absence of fluid over the upper margin of the patella in a sagittal image; Grade-1 signified some fluid above the upper margin of the patella but the length of the fluid column shorter than that of the patella; Grade-2 signified a fluid column above the upper margin of patella longer than the length of the patella; Grade-3 signified a fluid column above the upper margin of patella longer than the length of the patella with a thickness of ≥ 1cm. Intra-observer reliability was assessed in 50 MR images and yielded an ICC of 0.89-0.98. Pathological effusion was defined as any effusion score ≥2.

## 3.8 Radiology

A standing anteroposterior semiflexed x-ray of the right knee was taken in all subjects at visits 1 and 3. The angle was kept to 10–15˚ by a purpose built goniometer. The tube to film and tube to tibial plateau angle was 90˚. Daily quality assurance was performed on the equipment. Radiographs were scored individually for osteophytes and joint space narrowing (JSN), as described previously [84] (Figures 3.7, 3.8). Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial JSN, lateral JSN, medial osteophytes (femoral and tibial combined) and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International (OARSI) atlas [82]. A non-zero score in either JSN or osteophytosis was regarded as evidence of ROA. Reproducibility was assessed in 50 radiographs, two weeks apart, and yielded an ICC of 0.99 for osteophytes and 0.98 for JSN.

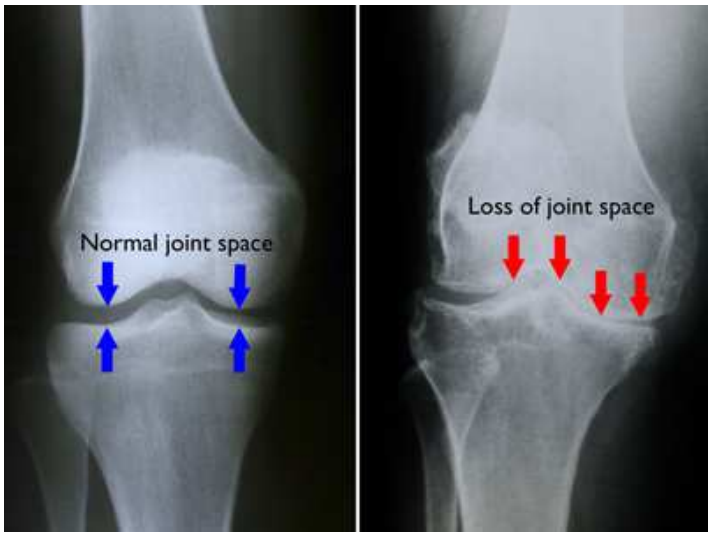


**Figure 3.7.** Joint space narrowing

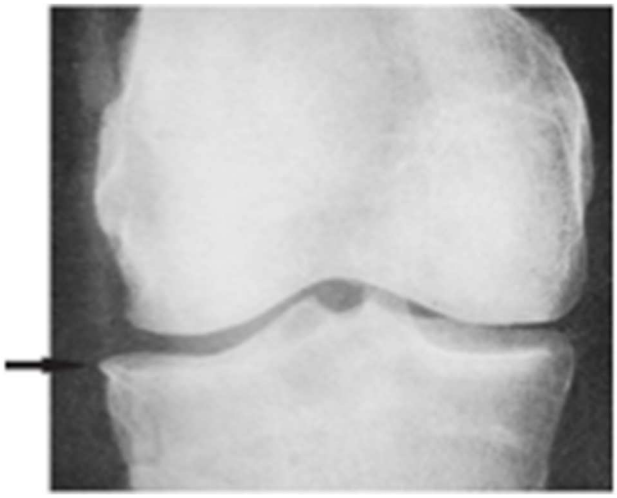

**Figure 3.8.** Osteophyte

## 3.9 Summary of outcome factors, study factors and covariates

Table 3.2 summarises the variables used in each chapter of this thesis.

**Table 3.2.** Summary of outcome factors, study factors, and covariates used in this thesis

| Chapter | Outcome factors | Study factors | Covariates |
|---|---|---|---|
| 4 | Cartilage volume, cartilage defects, BMLs, Meniscal tears/extrusion, bone area | Knee Injury | Age, sex, BMI, family history of OA |
| 5 | Cartilage volume loss, changes in JSN and osteophytes | Family history of OA | Age, sex, BMI, knee pain, bone area, cartilage defects and muscle strength |
| 6 | Change in BMLs | Family history of OA, knee pain, BMI, sex, physical activity | Age, cartilage defects, meniscal tears |
| 7 | Change in meniscal tears | Knee injury, Family history of OA, knee pain, cartilage volume, BMLs | Age, sex |
| 8 | Change in cartilage defects, cartilage volume loss | Family history of OA, knee pain | Age, sex, meniscal tears, meniscal extrusion, BMLs |
| 9 | Changes in JSN and osteophytes | Cartilage volume loss, changes in cartilage defects, meniscal tears and extrusion | Age, sex, BMI, family history of OA |

## 3.10 Sample size and role of the candidate in the Offspring study

As the Offspring study was in progress before commencement of the PhD candidature formal sample size calculations were not performed during the design of this thesis. Therefore, participant numbers in the analyses reported in this thesis were limited to the numbers recruited at baseline and follow-up, and to those who provided complete data for relevant outcome and study factors. As such, sample sizes vary between chapters, and the reasons for exclusion are described in each chapter. Nevertheless, it subsequently proved that sample sizes were more than adequate to answer the thesis research questions as this thesis has reported significant findings related to the research questions.

The candidate was involved in Offspring study data acquisition and collection, data management, analysis and interpretation of data, initial manuscript preparation and manuscript revision. Data acquisition was also completed prior to and during the candidature by a number

of other Offspring study staff members and volunteers, including Graeme Jones, Changhai Ding, Dawn Aitken, Flavia Cicuttini, Jean-Pierre Pelletier and Johanne Martel-Pelletier. Several colleagues had also begun analyses using Offspring study data before candidature was undertaken, and the candidate gratefully acknowledges their contribution.

## 3.11 Ethical considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants.

## 3.12 Statistical analysis

T-tests and chi-squared tests were used to compare differences in means and proportions as appropriate. A P value less than 0.05 (two-tailed) was considered statistically significant. A more detailed description of statistical analyses performed is presented in their relevant chapters. All statistical analyses were performed on Intercooled Stata V.12.0 for windows (StataCorp LP).

# CHAPTER FOUR

## History of Knee Injury and MRI-Assessed Knee Structures in Middle- and Older-Aged Adults: A Cross-Sectional Study

# 4.1 Introduction

Knee osteoarthritis (OA) is a major public health problem and a major cause of pain and disability in older people [115]. Although the pathogenesis and etiology of OA is not fully understood, it is regarded as an active process involving the whole joint [116].

History of joint injury is widely accepted as a contributory factor in the development of knee OA. There is some evidence to suggest that joint injury may lead to OA of other joints as well but it is less consistent compared to knee joint [117, 118]. Major trauma to the knee has the potential for damage to any of the knee structures which are important for joint homeostasis [55]. Several epidemiological studies have shown this association using radiography. Kellgren and Lawrence demonstrated the relation between joint injury and radiographic osteoarthritis (ROA) of the knee as early as 1958 [119]. Since then several cross-sectional [120] and case-control studies [121, 122] have confirmed the association between knee injury and subsequent ROA. In a prospective cohort study, Wilder *et al.* showed that individuals with a history of knee injury were 7.4 times more likely to develop knee ROA than individuals who did not have a history of knee injury [55]. More recently Toivanen *et al.* showed similar results in a 22 year follow-up study [123].

All the studies mentioned earlier have used radiography to assess OA. While radiography is the current gold standard for the diagnosis of OA, magnetic resonance imaging (MRI) is being increasingly used to study OA as it allows visualisation of the whole joint [124]. However, a lack of standard MRI criteria for OA has hampered its use in regular clinical practice and research. In a recent systematic review, leading experts defined OA criteria on MRI using a Delphi voting exercise [101]. Osteophytes, bone marrow lesions (BMLs), cartilage defects and meniscal tears were included in the criteria to define OA using MRI. Other structures such as cartilage loss and increased tibial bone area were not included in the criteria but commonly result from the above factors and have also been shown to predict total knee replacement (TKR) surgery [125, 126].

Despite the abundance of available literature showing the association between history of knee injury and ROA, there are still some deficiencies in our understanding of the exact causal relationship. Firstly, it’s not clear whether the injury to the knee joint or the subsequent surgery leads to the development of secondary OA, as the available literature often refers to

knee trauma without a clear distinction between the two [127, 128]. Secondly, it is not known which structures comprising the knee joint, as determined by MRI, are affected by injury and hence contribute towards the progression of the disease process.

The aim of this study, therefore, was to describe the cross-sectional association between history of knee injury and knee structures using MRI in a population-based cohort of middle-aged subjects and a randomly selected cohort of older subjects.

# 4.2 Methods

## 4.2.1 Subjects

This study was conducted as part of the Offspring Study [113] and the Tasmanian Older Adult Cohort (TASOAC) Study [129]; details for both studies have been published previously.

The Offspring study is an ongoing population-based study. This study includes data from Phase 1 of the Offspring study, which was carried out in southern Tasmania (primarily in the capital city of Hobart), between June 2000 and December 2001. Matched sampling was used to recruit the study participants (mean age 45 years, range 26–61; 58% females). Half of the participants were the adult children of patients who had had a knee replacement performed for idiopathic knee OA at any Hobart hospital between 1996 to 2000. Controls were randomly selected and matched by age and sex.

The Tasmanian Older Adult Cohort (TASOAC) study is an ongoing, prospective, population-based study aimed to examine OA progression. Men and women aged 50–80 years in 2002 were selected from the electoral roll in Southern Tasmania (population 229,000) using sex-stratified simple random sampling without replacement (response rate 57%). This study includes data from the first follow-up which was carried out after 2.6 years (mean age 63 years, age range 51-79, females 51 %) as the questionnaire at the baseline visit did not assess a history of knee injury.

Participants were excluded from both studies if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia) or were institutionalized. The studies were conducted in compliance with the Declaration of Helsinki and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. Written informed consent was obtained from all participants.

### 4.2.2 Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed), using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$).

### 4.2.3 Knee joint injury and surgery

History of knee joint injury and surgery were assessed using a self-administered questionnaire which included the following questions and was identical in both cohorts:

"Have you ever had a previous knee injury which resulted in non-weight bearing treatment for 24 hours or more?"

"If yes, then which knee?"

"Please provide further details about the injury"

"Have you ever had a knee surgery?"

"If yes, then which knee?"

"Please provide further details about the surgery"

Only right knee injuries were included in the analysis as MRI scans were on the right knee.

### 4.2.4 MRI

MRI scans of the right knee were performed in both studies. The following protocol was used in each study:

### 4.2.5 TASOAC

All knees were imaged in the sagittal plane on a 1.5T whole-body magnetic resonance unit (Picker, Cleveland, Ohio, USA). The following sequence and parameters were used: (1) a T1-weighted fat saturation three–dimensional (3D) gradient-recalled acquisition in the steady state, flip angle 30°, repetition time 31 ms, echo time 6.71 ms, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an interslice gap; and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228×256–pixel matrix, slice thickness of 4 mm with a interslice gap of 0.5–1.0 mm.

### 4.2.6 Offspring

All knees were imaged in the sagittal plane on a 1.5T whole-body MR unit (Signa Advantage HiSpeed; GE Medical Systems, Milwaukee, WI) using a commercial transmit–receive extremity coil. The following sequence and parameters were used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 msec, echo time 12 msec, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an interslice gap; and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256 × 256 matrix, slice thickness of 4 mm with an interslice gap of 0.5–1.0 mm.

### 4.2.7 Cartilage volume

Tibial cartilage volume was assessed by a trained observer on T1-weighted MR images using Osiris (University of Geneva, Geneva, Switzerland) software as previously described [104]. The image data were transferred to the workstation. The volumes of individual cartilage plates (medial tibial, lateral tibial and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 µm and 1.5mm thickness, continuous sections) for the final 3D

rendering using Osiris software. The coefficient of variation (CV) for both studies ranged between 2.1–2.2% for intra-observer repeatability [84, 104]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Quebec, Canada), as previously described [110, 112, 130]. First, using a semi-automated image-processing (segmentation), the whole cartilage geometry is extracted from MR sagittal range images. For each sagittal image in the volume data set, semi-automatic delineation is performed using an active-contour-segmentation technique. These initial contour lines are then automatically adjusted by using a 2D/3D, active-contour process (snake) to more closely fit the cartilage margins with sub-pixel accuracy, as already described [131]. The CV for both studies was approximately 2% for intra-observer and inter-scan repeatability [130].

### 4.2.8 Cartilage defects

Cartilage defects were assessed on T1-weighted MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, as previously described [113] as follows: grade 0=normal cartilage; grade 1=focal blistering and intracartilaginous low-signal intensity area with an intact surface and base; grade 2=irregularities on the surface or base and loss of thickness <50%; grade 3=deep ulceration with loss of thickness >50%; and grade 4=full-thickness chondral wear with exposure of subchondral bone. For the purpose of analysis in this study, cartilage defects were used as a dichotomous variable signifying presence or absence of any cartilage defect at a given site. Intraobserver reliability (expressed as intraclass correlation coefficient (ICC)) was 0.90 for the medial tibiofemoral compartment and 0.89 for the lateral tibiofemoral compartment for both studies. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.90 for the medial tibiofemoral compartment and 0.85 for the lateral tibiofemoral compartment [113].

### 4.2.9 Bone marrow lesions

BMLs were assessed on T2-weighted MR images and defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites. For the purpose of analysis, BMLs were used as a dichotomous variable

signifying the presence or absence of any BMLs regardless of the site. The ICC was 0.97 for intra-observer repeatability in TASOAC [93] and ranged from 0.89 to 1.00 in the Offspring study [106].

### 4.2.10 Tibial bone area

Knee tibial plateau bone area was assessed on T1-weighted MR images and determined by means of image processing on an independent workstation using the software program Osiris (University of Geneva) as previously described [84, 89, 132]. To transform the images from the sagittal plane to the axial plane, the Analyse Software package developed by the Mayo Clinic was employed. Medial and lateral tibial plateau bone area was determined by creating an isotropic volume from the three input images closest to the knee joint. The bone area of the medial and lateral tibial plateau was then directly measured from the reformatted axial images. The CV was 2.2–2.6% for intra- observer repeatability [84].

### 4.2.11 Meniscal damage

Meniscal damage was assessed by a trained observer on T1-weighted MR images as previously described [110]. The proportion of the menisci affected by a tear, partial or full extrusion was scored separately (yes/no) at the anterior, middle, and posterior horns (medially/laterally). Anterior, middle and posterior scores were summed to get medial and lateral meniscal tear/extrusion scores. For the purpose of analysis, a dichotomous score was used which signified the presence or absence of any tear or extrusion at specific sites. The intra- and inter-observer correlation coefficient ranged from 0.86 to 0.96 for meniscal tear and 0.85 to 0.92 for meniscal extrusion [111].

### 4.2.12 Data analysis

Descriptive statistics of characteristics of the sample were tabulated. Regression analyses were used to examine the association between history of knee injury and each knee structure. Cartilage volume and tibial bone area were analysed as continuous variables whereas

cartilage defects, bone marrow lesions and meniscal pathology were analysed as dichotomised variables. Both continuous measures were analysed using linear regression analysis whereas the three dichotomised variables were analysed using log binomial regression analysis. Mean values of continuous variables and percentages (with exact numbers in the form of fractions) are provided for both injured and non-injured group in all the tables. Differences of means (DM) and prevalence ratios (PR) were used to express continuous and dichotomised variables respectively. Analyses were adjusted for age, sex, height and weight. Further adjustment for knee surgery was also performed. Offspring-control interactions in Offspring study and sex interactions in both studies were explored for all the associations between history of knee injury and knee structures. Additional analysis examined the association between history of knee surgery and each knee structure.

A p value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata V.12.0 for windows (StataCorp LP).

## 4.3 Results

A total of 802 participants (Offspring =372; TASOAC=430) were included in this study. Table 4.1 describes the characteristics of the two study populations.

**Table 4.1.** Characteristics of the study participants

| | OFFSPRING | TASOAC |
|---|---|---|
| No of participants | 372 | 430 |
| Female | 58% | 51% |
| Age | 45 (26-61) | 63 (51-79) |
| BMI | 27.0 (4.7) | 27.8 (4.8) |
| Any joint space narrowing | 14% | 59% |
| Any osteophytes | 7% | 10% |
| History of knee injury | 19% | 12% |
| History of knee surgery | 6% | 12% |

Participants in TASOAC study were older compared to the Offspring study. TASOAC had approximately the same proportion of male and female participants, whereas the Offspring study had a higher proportion of female participants. BMI in both cohorts was in the overweight range and as expected the older cohort had a higher percentage of participants with JSN and osteophytes. Participants in the Offspring study, despite being younger, had a higher proportion report a history of knee injury.

Table 4.2 describes the association between knee injury and cartilage volume. In the Offspring study, participants with a history of knee injury had higher mean cartilage volume compared to participants in the non-injured group. However, after adjustment for age, sex, height and weight, the association did not persist. In TASOAC, participants in the injured

group had a lower adjusted knee cartilage volume but the difference was statistically significant at the lateral tibial and the total tibial sites only.

**Table 4.2.** Association between injury and cartilage volume in the knee

| Cartilage Volume (site) | Injury Mean Vol ($mm^3$) | No Injury Mean Vol ($mm^3$) | Unadjusted DM (95%CI) | Adjusted* DM (95%CI) |
|---|---|---|---|---|
| **Offspring** | | | | |
| Medial Tibial | 2436 | 2184 | **+252 (108,396)** | +54 (-63,+170) |
| Lateral Tibial | 2828 | 2553 | **+278 (106,450)** | +12 (-115,+138) |
| Total Tibial | 5264 | 4734 | **+530 (231,829)** | +67 (-152,+286) |
| Medial Femoral | 4892 | 4500 | **+391 (10,772)** | +79 (-211,+369) |
| Lateral Femoral | 5142 | 4649 | **+492 (108,877)** | +125 (-125,+375) |
| Total Femoral | 10034 | 9150 | **+884 (162,1605)** | +204 (-275,+683) |
| Total Knee | 15205 | 13925 | **+1280 (228,2332)** | +298 (-391,+987) |
| **TASOAC** | | | | |
| Medial Tibial | 2108 | 2149 | -41 (-221,+139) | -59 (-198,+79) |
| Lateral Tibial | 2402 | 2627 | -224 (-463,+15) | **-265 (-439,-92)** |
| Total Tibial | 4510 | 4776 | -265(-657,+199) | **-325 (-600,-51)** |
| Medial Femoral | 3882 | 3857 | +26 (-407,+459) | -93 (-369,+183) |
| Lateral Femoral | 4280 | 4229 | +51 (-400,+502) | -69 (-325,+188) |
| Total Femoral | 8163 | 8086 | +77 (-778,+932) | -162 (-645,+322) |
| Total Knee | 12663 | 12910 | -246(-1493,+1000) | -429(-1100,+241) |

DM-Difference of means
CI-Confidence Interval
*Adjusted for age, sex, height and weight

Table 4.3 describes the association between knee injury and cartilage defects. Overall, those in the injured group had a higher percentage of cartilage defects compared to the non-injured group. These differences were significant for the TASOAC participants at the medial tibial, lateral tibial, lateral femoral and total cartilage sites after adjustment. Prevalence ratios for Offspring study were all weaker and non-significant.

**Table 4.3.** Association between injury and cartilage defects in the knee

| Cartilage Defects Absent/Present(site) | Injury % (n/N) | No Injury % (n/N) | Unadjusted PR (95%CI) | Adjusted* PR (95%CI) |
|---|---|---|---|---|
| **Offspring** | | | | |
| Medial Tibial | 19%(14/71) | 12% (35/299) | 1.7 (0.9,2.9) | 1.6 (0.9,2.8) |
| Lateral Tibial | 15% (11/72) | 14% (43/299) | 1.1 (0.6,2.0) | 0.9 (0.5,1.7) |
| Medial Femoral | 8% (6/72) | 6% (18/299) | 1.4 (0.6,3.4) | 1.4 (0.5,3.5) |
| Lateral Femoral | 6% (4/72) | 6% (19/299) | 0.9 (0.3,2.5) | 0.8 (0.3,2.5) |
| Total Knee | 31% (22/72) | 27% (82/299) | 1.1 (0.8,1.7) | 1.0 (0.7,1.5) |
| **TASOAC** | | | | |
| Medial Tibial | 41% (16/39) | 19% (69/373) | **2.2 (1.4,3.4)** | **2.3 (1.5,3.4)** |
| Lateral Tibial | 44% (17/39) | 28% (104/373) | **1.6 (1.1,2.3)** | **1.6 (1.1,2.4)** |
| Medial Femoral | 44% (17/39) | 29% (109/373) | **1.5 (1.0,2.2)** | 1.4 (0.9,2.1) |
| Lateral Femoral | 31% (12/39) | 14% (53/373) | **2.2 (1.3,3.7)** | **2.1 (1.3,3.5)** |
| Total Knee | 64% (25/39) | 50% (186/373) | 1.3 (0.9,1.6) | **1.3 (1.0,1.7)** |

PR-Prevalence Ratio
CI-Confidence Interval
*Adjusted for age, sex, height and weight

Table 4.4 describes the association between knee injury and BMLs. In both cohorts those in the injured group had a higher percentage of BMLs present compared to the non-injured group and significant associations were seen at the medial tibial, medial femoral and total sites in both unadjusted and adjusted analysis.

**Table 4.4.** Association between injury and bone marrow lesions in the knee

| BMLs Absent/Present(site) | Injury % (n/N) | No Injury % (n/N) | Unadjusted PR (95%CI) | Adjusted* PR (95%CI) |
|---|---|---|---|---|
| **Offspring** | | | | |
| Medial Tibial | 33% (13/39) | 16% (25/159) | **2.1 (1.2,3.8)** | **2.1 (1.2,3.7)** |
| Lateral Tibial | 31% (12/39) | 25% (40/161) | 1.2 (0.7,2.1) | 1.3 (0.8,2.3) |
| Medial Femoral | 31% (12/39) | 11% (17/160) | **2.9 (1.5,5.6)** | **2.6 (1.3,5.4)** |
| Lateral Femoral | 21% (8/39) | 14% (23/159) | 1.4 (0.7,2.9) | 1.5 (0.7,3.2) |
| Total Knee | 72% (28/39) | 49% (82/158) | **1.5 (1.1,1.9)** | **1.6 (1.2,2.1)** |
| **TASOAC** | | | | |
| Medial Tibial | 33% (15/46) | 18% (63/346) | **1.9 (1.1,3.1)** | **1.8 (1.1,3.0)** |
| Lateral Tibial | 17% (8/46) | 15% (51/346) | 1.5 (0.8,3.0) | 1.6 (0.8,3.1) |
| Medial Femoral | 17% (8/46) | 12% (40/346) | **2.0 (1.0,3.9)** | **1.9 (1.0,3.5)** |
| Lateral Femoral | 30% (14/46) | 17% (58/346) | 1.7 (0.9,3.0) | 1.7 (0.9,3.0) |
| Total Knee | 52% (24/46) | 41% (143/346) | **1.4 (1.1,1.9)** | **1.4 (1.0,1.9)** |

PR-Prevalence Ratio
CI-Confidence Interval
*Adjusted for age, sex, height and weight

Table 4.5 describes the association between knee injury and tibial bone area. In both cohorts, those in the injured group had a higher tibial bone area after adjustment for age, sex, height and weight. In the Offspring study, there was a significant association between the history of knee injury and the tibial bone area at all sites in adjusted analysis. In TASOAC, there was a significant association at medial and total tibial bone area sites in adjusted analysis.

**Table 4.5.** Association between injury and tibial bone area in the knee

| Bone Area (site) | Injury Mean area($mm^2$) | No Injury Mean area($mm^2$) | Unadjusted DM(95%CI) | Adjusted* DM(95%CI) |
|---|---|---|---|---|
| **Offspring** | | | | |
| Medial | 1874 | 1711 | +**162(+91,+233)** | **+49(+7,+91)** |
| Lateral | 1293 | 1178 | **+116(+63,+168)** | **+37(+4,+71)** |
| Total | 3167 | 2889 | +**278(+261,+395)** | **+86(+23,+149)** |
| **TASOAC** | | | | |
| Medial | 2137 | 2133 | +3(-156,+163) | **+91(+4,+178)** |
| Lateral | 1226 | 1238 | -12(-125,+101) | +49(-11,+109) |
| Total | 3362 | 3370 | -8(-269,+251) | **+140(+19,+260)** |

DM-Difference of means
CI-Confidence Interval
*Adjusted for age, sex, height and weight

Table 4.6 describes the association between meniscal pathology and knee injury. Meniscal tears were very common in both cohorts and there was no difference in the prevalence of tears in injured compared to non-injured groups. Table 4.6 presents results for medial meniscal extrusions only as lateral meniscal extrusions were extremely rare in both cohorts. There was a higher percentage of participants with medial meniscal extrusions in the injured group in both cohorts; however, the difference was statistically significant for the Offspring study only.

**Table 4.6.** Association between injury and meniscal pathology in the knee

| Meniscal Pathology | Injury % (n/N) | No Injury % (n/N) | Unadjusted PR (95%CI) | Adjusted* PR (95%CI) |
|---|---|---|---|---|
| **Offspring** | | | | |
| Medial Tear | 68%(41/60) | 58%(138/238) | 1.2 (0.9, 1.4) | 1.2 (0.9, 1.5) |
| Lateral Tear | 48%(29/60) | 52%(124/238) | 0.9 (0.7, 1.2) | 0.9 (0.7, 1.3) |
| Medial Extrusion | 13%(8/60) | 5%(13/238) | **2.4 (1.1, 5.6)** | **2.7 (1.1, 6.8)** |
| **TASOAC** | | | | |
| Medial Tear | 100%(29/29) | 99%(289/290) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.0) |
| Lateral Tear | 100%(29/29) | 99%(289/290) | 1.0 (0.9, 1.1) | 1.0 (0.9, 1.0) |
| Medial Extrusion | 28%(8/29) | 17%(50/290) | 1.6 (0.8, 3.0) | 1.6 (0.8, 3.0) |

PR-Prevalence Ratio
CI-Confidence Interval
*Adjusted for age, sex, height and weight

Further adjustment for history of knee surgery did not change the effect size for any of the associations mentioned above.

There was no offspring-control or sex interaction for any of the above mentioned associations in the Offspring cohort. There was no sex-interaction in the TASOAC cohort for all the above mentioned associations except for the lateral tibial cartilage volume and lateral tibial cartilage defects sites, where male participants with a history of knee injury were losing significantly more cartilage volume and had more cartilage defects compared to female participants.

Additional analysis was performed to examine the association between history of knee surgery and each knee structure. There were no significant associations between the history of knee surgery and any knee structures in the Offspring study. In TASOAC, history of knee surgery was independently associated with a higher prevalence of cartilage defects at all sites (highest prevalence ratio at the lateral femoral site: PR=2.9(1.9-4.5)), higher lateral tibial bone area (DM= +29 (+3, +56)) and a higher prevalence of medial (PR=1.1 (1.0, 1.1) and lateral (PR=1.1 (1.0, 1.1) meniscal tears (after taking a history of knee injury, age, sex, weight and height into account).

## 4.4 Discussion

To the best of our knowledge, this is the first paper to describe the association between history of knee injury and global knee structural damage using MRI. The prevalence of BML's and tibial bone area was higher in those with a history of knee injury and this was seen in both cohorts. Medial meniscal extrusion presence was higher in those with a history of knee injury in the middle-aged cohort only, whereas cartilage defects and cartilage volume (lateral and total tibial only) were significantly associated with knee injury in the older-aged cohort. Meniscal tears showed no significant associations in either cohort.

Bone marrow lesions are known to be a consequence of acute injury and trauma, especially after fractures [133] and anterior cruciate ligament (ACL) rupture [134]. Very few studies have looked at the long term risk of developing BMLs after a knee injury. In a recent study, Frobell *et al.* [135] followed 61 patients for 2 years after acute ACL disruption who were either treated with early/late ACL reconstruction or with conservative rehabilitation. They found that lateral compartment BMLs sustained after ACL rupture, completely resolved after 2 years in almost all patients but 34 % patients developed new BMLs over the 2 years follow-up period. In our study there were no significant differences in the lateral compartment between the injured and the non-injured groups in both cohorts but we did see an approximate doubling of prevalence in the medial compartment, a site which is of greater relevance to OA in older adults [136]. Data from this study suggests that age may not play a major role in the association between knee injury and BMLs as we saw very similar trends in both cohorts at all sites.

Tibial plateau bone area is associated with knee OA with increases in bone area predicting increased JSN, osteophyte development and cartilage loss on MRI [137]. To the best of our knowledge, no study has examined the association between history of knee injury and tibial bone area. Data from this study shows that history of knee injury is significantly associated with increased tibial bone area and this may reflect an attempt by subchondral bone to repair. Age may not play a crucial role in mediating this association as total tibial bone area was significantly associated with injury in both cohorts, although the effect size was consistently larger in the older cohort possibly reflecting the increased time since the injury.

Several studies have examined the association between cartilage defects/loss and history of knee surgery [138]; however, there is limited data showing the same association with knee injury. Elsaid *et al.* have shown in a rabbit injury model that knee injury can result in loss of boundary-lubricating ability of synovial fluid which can cause damage to the articular cartilage matrix [139]. In a 7-10 year follow-up study, Crema *et al.* found that knee trauma, either surgical or non-surgical, was associated with cartilage degenerative changes in only a minority of patients and very few patients with a complete ACL tear at baseline showed cartilage loss at follow-up [140]. We found significant associations between cartilage defects and history of knee injury at almost all sites in the older cohort but this was not the case for the middle-aged cohort. This appears consistent with the Crema *et al.* findings as their study population had an average age of approximately 34 years. Very few patients in their study showed cartilage loss after a complete ACL tear. Similarly, we did not find consistent associations between history of knee injury and cartilage volume with the lateral and total tibial cartilage volume sites associated with knee injury in the older cohort only. This possibly reflects changes in the ability of cartilage to repair given that cartilage defects in the middle-aged adults can improve with time [89] but such improvement in cartilage defect grade is very rare in older adults [141]. Cartilage defects are associated with cartilage loss [113], so it is plausible that the associations we saw for reduced cartilage volume were also mediated by cartilage defects or that other structural changes result in cartilage loss in later life.

There was a significant association between the history of knee injury and meniscal extrusions in the middle-aged cohort only but no significant associations for meniscal tears in either cohort. In a 30 month prospective study, Englund *et al.* found a strong association between meniscal pathology (tears and extrusions combined) and knee injury OR=4.14 (95% CI 2.06 to 8.31) [142].We analysed tears and extrusions separately as both cohorts had a very high prevalence of meniscal tears which would have then affected the meniscal extrusion findings. Age may not affect the associations for meniscal tears/extrusions as there was no difference in the prevalence of tears between injured and non-injured groups in either cohort and our data suggests that tears become more prevalent with age regardless of knee injury.

History of knee surgery seems to be more important in the older adults for knee structural pathologies. We did not observe any significant associations in the middle-aged cohort but

this could possibly be explained by the fact that only 6% of the middle-aged participants reported undergoing any knee surgical procedure compared to 12% of the older participants. Interestingly meniscal tears, despite having a very high prevalence, showed a modest but a significant association with the history of knee surgery. Our data from the two cohorts suggests that the prevalence of meniscal tears increases with age but knee surgery probably does play a role as well. Cartilage defects were the only structural pathology which was consistently associated with both knee injury and surgery in the older adults, again highlighting the possibility of reparative potential in the younger age groups.

This study has strengths and limitations. A strength includes the use of MRI to assess knee structure and the consistent method of defining knee injury across both cohorts. The MRI readers who performed the scoring in this study have all undergone extensive training and demonstrate significant expertise and experience in scoring MRI features. They have consulted and been advised by radiologists specialized in musculoskeletal imaging. Moreover, and as noted in the manuscript, the reproducibility is high for all the MRI measures. Limitations include, firstly the cross-sectional design which does not give information about causality although injury preceded the MRI in all subjects. Secondly, the use of a questionnaire to assess injury can potentially lead to errors in recall especially in older patients who might have had a knee injury several decades ago. The older cohort in this study had a lower prevalence of history of knee injury, which could be due to recall bias but could also be a result of random variation between the cohorts. Other studies investigating the role of history of knee injury in the development of OA have used structural changes like ACL damage, meniscal tears and bone marrow lesions as markers of knee injury[143, 144]. These structural changes, although objective, are changes because of injury and not the primary injury itself. Furthermore these structural changes can be degenerative in nature and can occur without knee injury in association with other structural changes as part of an active OA process [93, 94]. Thirdly, the definition of knee injury varies considerably amongst studies as there is no standard definition of knee injury. Some studies have used similar definitions to ours including non-weight bearing as a criterion for a significant knee injury however the duration of non-weight bearing seems variable across studies. Other studies have used outcomes such as duration of pain after the injury as a criteria for a significant injury [128]. Therefore, our definition may have affected our findings; nonetheless we have

demonstrated biologically plausible associations in both cohorts. Fourthly, we did not have any information about the time from injury which can potentially be an important factor when assessing the severity of structural damage [145].

## Conclusion

The association between knee injury and MRI-assessed structural pathology in the knee joint is moderate and appears to be stronger in older adults compared to middle aged adults.

# CHAPTER FIVE

## A Family History of Knee Joint Replacement Increases the Progression of Knee Radiographic Osteoarthritis and Medial Tibial Cartilage Volume Loss Over 10 Years

# 5.1 Introduction

Osteoarthritis (OA) is a slowly developing chronic disease that has a multifactorial origin with the knee being the most commonly affected joint [115]. The pathogenesis of OA is not fully understood but some of the factors which contribute towards the development of OA include genetics, obesity, joint injury and occupational factors [68]. There is strong evidence that genetic factors play an important role in radiographic OA (ROA) of the hands and the spine [68, 69]. A cross-sectional study [70] using the present cohort showed a significant genetic contribution to the severity but not prevalence of knee ROA but the evidence is inconsistent for knee ROA [68-72]. This may reflect the difficulty to target specific genes. A recent meta-analysis of 9 genome-wide association studies including 5636 knee OA patients and 16972 controls, found that only 2 out of 199 published candidate OA genes had any significant association with OA [146]. The inconsistency may be due to different study designs [146], inherent measurement error associated with diagnosis of ROA, short follow-up periods and varying levels of genetic susceptibility of different phenotypic components of knee OA [147, 148].

Magnetic resonance imaging (MRI) is being increasingly used to study OA as it allows visualisation of the whole joint [124]. It is possible that different structures comprising the knee joint are under separate genetic influences. Twin studies have already shown high heritability estimates for cartilage volume in all compartments of the knee joint [149]. Previous work using the present cohort has also shown high heritability estimates for tibial and patellar cartilage volume [70] and a significant genetic contribution to medial tibial cartilage loss over 2 years [150]. Along with cartilage volume loss, change in cartilage defects, tibial bone area and quadriceps muscle strength were all shown to be under genetic influence [150]. All these structural changes are thought to contribute towards the progression of the disease, but a limitation in the design of these studies [70, 150] was the lack of radiographs at two years as it was not expected to see any major changes on radiographs in this time frame in a middle-aged population.

The aim of this population-based longitudinal study was therefore to describe the 10 year change in knee ROA and cartilage volume loss between offspring having at least one parent

with a total knee replacement for severe primary knee OA, and age- and sex-matched controls with no family history of knee OA.

## 5.2 Methods

### 5.2.1 Study subjects

This study was conducted as part of the Offspring study, which is an ongoing population-based study. The Offspring study began in southern Tasmania (primarily in the city of Hobart) in June 2000. Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000 [102]. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiographs when possible. The other half were age and sex matched controls, randomly selected from the population with no history of knee OA in either parent. This study includes data from the baseline visit, 2 year and 10 year follow up.

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants. Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). Participants were also excluded if they had undergone a knee replacement surgery or did so after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

### 5.2.2 Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$).

### 5.2.3 Knee pain

Knee pain was assessed using an interviewer administered questionnaire as described previously [102]. All the participants were asked the following question:

Have you had knee pain for more than 24 hours in the last 12 months or daily pain on greater than 30 days in the last year?

### 5.2.4 Leg strength

Muscle strength was measured by dynamometry at the lower limb (involving both legs simultaneously). This primarily involves the hip flexors and knee extensors. The participants were instructed in each technique prior to testing, and each measure was performed twice. The repeatability estimate (Cronbach's alpha) was 0.91 [70]. The device was calibrated by suspending known weights at regular intervals.

### 5.2.5 Magnetic resonance imaging

MRI of the right knee was performed as described previously [89, 104, 108]. Knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Picker International, USA) using a commercial transmit-receive extremity coil at the baseline visit, 2 year and 10 year follow up. The following image sequence was used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 msec, echo time 12 msec, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an interslice-gap (at all three visits); and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256×256 matrix, slice thickness of 4 mm with an interslice gap of 0.5–1.0 mm (at visit 2 and 3).

The same scanner (same model and machine) was used at all the three visits for both T1-weighted fat-suppressed and T2-weighted fat saturation images.

Cartilage volume:

Knee cartilage volume was evaluated at baseline and 10 years by a trained observer on T1-weighted gradient echo MR images. Knee cartilage volume was determined by means of image processing on an independent workstation at baseline and follow up. The volumes of

individual cartilage plates (medial tibia and femora, and lateral tibia and femora) were isolated from the total volume by manually drawing dis-articulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 × 312 μm by 1.5 mm thickness, continuous sections) for the final three-dimensional rendering to calculate the cartilage volume.

Tibial cartilage volume was assessed using Osiris (University of Geneva, Switzerland) software as previously described [104, 109]. The coefficient of variation(CV) ranged from 2.1–2.2% for intra-observer repeatability [84]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Canada), as previously described [110-112]. The CV was approximately 2% for intra-observer and inter-scan repeatability [111]. Total cartilage volume was calculated as: tibial + femoral cartilage volume.

Change in cartilage volume was calculated as: follow-up total cartilage volume - baseline total cartilage volume.

Readers were not blinded to the chronological sequence of the scans to reduce measurement error.

### 5.2.6 Cartilage defects

Cartilage defects were assessed on T1-weighted gradient echo MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites on a 0-4 scale, as previously described [113]: grade 0=normal cartilage; grade 1=focal blistering and intra-cartilaginous low-signal intensity area with an intact surface and base; grade 2=irregularities on the surface or base and loss of thickness <50%; grade 3=deep ulceration with loss of thickness >50%; and grade 4=full-thickness chondral wear with exposure of subchondral bone. Intraobserver reliability (expressed as intraclass correlation coefficient(ICC)) ranged from 0.89-0.90. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.85-0.90 [113]

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### 5.2.7 Bone area

The following measures of bone size were determined: total patella bone volume, and medial and lateral tibial plateau areas as described previously [104]. Contours were drawn around the patella in images 1.5 mm apart on sagittal views. Total volume was calculated for the patella due to its irregular shape, which made it difficult to identify a simpler, representative measure of patella size. Medial and lateral tibial plateau area was determined by creating an isotropic volume from the 3 input images closest to the joint after reformatting in the axial plane. The areas of the medial and lateral tibial plateaus were then directly measured from these images. The CV was 2.2% for the patella, 2.3% for the medial tibial plateau, and 2.4% for the lateral tibial plateau [104].

### 5.2.8 Meniscal tears

Meniscal tears were assessed by a trained observer on T1-weighted gradient echo and T2-weighted (side by side) MR images at visit-2 and 3 of the study as previously described [151]. The proportion of the menisci affected by a tear was scored separately (0-2 scale; 0=absence of a tear, 1=simple tear of different types: longitudinal, oblique, radial or horizontal, 2=complex tear signifying loss>50% area of meniscal tissue) at the anterior, middle, and posterior horns. Anterior, middle and posterior scores were summed to create medial and lateral meniscal tear scores. The intra- and inter-observer correlation coefficient ranged from 0.86 to 0.96 [111]. Meniscal tears were measured at visits 2 and 3 of the Offspring study, 2 and 10 years after the baseline visit.

### 5.2.9 Bone marrow lesions

Bone marrow lesions (BMLs) were assessed on fat suppressed T2-weighted MR images as described previously [93]. BMLs were defined as areas of increased signal intensity in the sub-chondral bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patellar and inferior patellar sites. One trained observer scored the BMLs by measuring the maximum area of the lesion in a specific compartment. The observer manually selected the

MRI slice with the greatest BML size. The BML with the highest score was used if more than one lesion was present at the same site. The ICC was 0.97. BMLs were measured at phase 2 of the Offspring study, 2 years after the baseline visit.

### 5.2.10 Radiology

A standing anteroposterior semiflexed x-ray of the right knee was taken in all subjects at baseline and 10 years. The angle was kept to 10–15˚ by a purpose built goniometer. The tube to film and tube to tibial plateau angle was 90˚. Daily quality assurance was performed on the equipment. Radiographs were scored individually for osteophytes and joint space narrowing (JSN), as described previously [84]. Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial JSN, lateral JSN, medial osteophytes (femoral and tibial combined) and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers (LC, AM) simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International (OARSI) atlas [82]. A non-zero score in either JSN or osteophytosis was regarded as evidence of ROA. Reproducibility was assessed in 50 radiographs, two weeks apart, and yielded an ICC of 0.99 for osteophytes and 0.98 for JSN.

Change in ROA was calculated as: follow-up ROA score - baseline ROA score.

Readers were not blinded to the chronological sequence of the scans to reduce measurement error.

### 5.2.11 Statistical analysis

This study was no longer paired as matching is no longer possible due to loss to follow up.

T-tests were used to describe the differences in baseline characteristics and ROA/cartilage volume loss over 10 years between offspring and controls. Negative binomial and linear regression were used to describe radiographic changes (expressed as difference in ratios (dr)) and cartilage loss (expressed as difference in means (dm)) respectively. Multivariable

analyses were first adjusted for age, sex and the corresponding baseline measures (i.e. baseline cartilage volume for cartilage loss). We then adjusted for the five baseline measures which were significantly different between offspring and controls in the original whole sample using conditional logistic regression (BMI, knee pain, cartilage defects, bone size and leg strength) [102, 152] in order to examine potential mediators. Further analysis was done to explore any sex interaction within offspring and control groups for ROA changes and cartilage volume loss in the multivariable models.

A p-value less than 0.05 (two-tailed) was considered statistically significant. All analyses were performed on Intercooled Stata V.12.0 for windows (StataCorp LP).

## 5.3 Results

Of the 371 participants included in the Offspring study, 220 between the ages of 26 and 61 years were followed up for 10 years. None of the participants who were lost to follow-up underwent a knee replacement surgery. Table 5.1 describes the baseline characteristics of participants who were followed up (220) compared to participants who were lost to follow up (151). There were no significant differences between the two groups except for a higher lateral tibial bone area in the participants who were followed up.

Table 5.2 describes baseline characteristics of the offspring (n=115) and controls (n=105). The mean age of both offspring and controls at baseline was approximately 45 years and both groups had a higher proportion of female participants. Prevalence of ROA at baseline was low in both groups without any significant differences between the two groups. Offspring had a slightly but significantly higher BMI, higher lateral femoral cartilage volume, knee pain prevalence and total cartilage defects score compared to controls.

Comparison between offspring and controls (Table 5.3) for radiographic score changes revealed that offspring had a significantly greater increase in medial JSN, total medial osteophytes, total lateral osteophytes, total osteophytes and total ROA scores. There was no significant difference in lateral and total JSN scores. For cartilage volume loss (Table 5.3), offspring had a significantly greater loss at the medial tibial site only. There was no significant difference in cartilage volume loss at lateral tibial, medial femoral, lateral femoral and patellar sites.

Multivariable comparison (Table 5.4) between offspring and controls for radiographic score changes revealed that after adjustment for age, sex and the corresponding baseline measures, offspring had a greater increase in medial JSN, total medial osteophytes, total lateral osteophytes, total osteophytes and total ROA scores. However, after further adjustment for the baseline factors, which were significantly different between offspring and controls, the difference in ratios remained significantly greater only for medial JSN score. Further adjustment for medial meniscal tears (measured at 2 year) had no effect; however adjustment for medial (tibial + femoral) BMLs (measured at 2 years) changed the effect size by more than 10% [(dr = +1.63 (+0.84, +3.03)]. For absolute cartilage volume loss (Table 5.4), difference in means at the medial tibial site became non-significant (p=0.054) after adjusting

for age, sex and corresponding baseline measure and remained so after further adjustment for differences in baseline factors (p=0.055).

**Table 5.1.** Baseline characteristics of the participants who were followed-up and who were lost to follow up

| Characteristic | Follow-up (n = 220) | Loss Follow-up (n = 151) | P-value |
|---|---|---|---|
| Age (years) | 45.3 ± 6.7 | 45.1 ± 7.2 | 0.806 |
| Female (%) | 58 | 59 | 0.749* |
| BMI (kg/m$^2$) | 27.2 ± 4.9 | 26.8 ± 4.3 | 0.499 |
| Offspring (%) | 52 | 47 | 0.891 |
| Radiographic OA (%) | 18 | 15 | 0.486* |
| Knee pain present (%) | 33 | 34 | 0.917* |
| Medial tibial cartilage volume (mm$^3$) | 2234.1 ± 547.3 | 2230.8 ± 585.3 | 0.956 |
| Lateral tibial cartilage volume (mm$^3$) | 2620.9 ± 671.3 | 2579.3 ± 680.9 | 0.561 |
| Medial femoral cartilage volume (mm$^3$) | 4594.8 ± 1295.2 | 4541.4 ± 1145.1 | 0.734 |
| Lateral femoral cartilage volume (mm$^3$) | 4753.6 ± 1268.3 | 4719.6 ± 1252.0 | 0.836 |
| Patellar cartilage volume (mm$^3$) | 3480.2 ± 976.3 | 3430.3 ± 975.1 | 0.629 |
| Medial tibial cartilage defects | 1.2 ± 0.4 | 1.2 ± 0.4 | 0.697 |
| Lateral tibial cartilage defects | 1.2 ± 0.4 | 1.2 ± 0.4 | 0.948 |
| Medial femoral cartilage defects | 0.9 ± 0.5 | 1.0 ± 0.5 | 0.443 |
| Lateral femoral cartilage defects | 0.9 ± 0.5 | 0.9 ± 0.5 | 0.526 |
| Patellar cartilage defects | 1.2 ± 0.9 | 1.2 ± 1.1 | 0.987 |
| Medial tibial bone area (cm$^2$) | 17.6 ± 2.8 | 17.1 ± 2.6 | 0.092 |
| Lateral tibial bone area (cm$^2$) | **12.2 ± 2.1** | **11.7 ± 1.9** | **0.027** |
| Patellar bone volume (cm$^3$) | 13.9 ± 3.3 | 13.5 ± 3.3 | 0.279 |

Mean ± standard deviation except for percentages; *Determined by Chi square test, others by t-test

**Table 5.2.** Baseline characteristics of the study participants

| | **Offspring (N=115)** | **Controls (N=105)** | **P-Value** |
|---|---|---|---|
| Age (years) | 44.8 ±6.8 | 45.8 ±6.5 | 0.261 |
| Female (%) | 55% | 60% | 0.436 |
| BMI (kg/m$^2$)* | **27.9 ±5.3** | **26.3 ±4.5** | **0.018** |
| Any ROA (%) | 18% | 17% | 0.894 |
| Any medial JSN (%) | 14% | 14% | 0.937 |
| Any lateral JSN (%) | 3% | 4% | 0.907 |
| Any tibial osteophytes (%) | 15% | 8% | 0.199 |
| Any femoral osteophytes (%) | 14% | 4% | 0.052 |
| Medial tibial cartilage volume (mm$^3$) | 2271 ±46 | 2194 ±59 | 0.295 |
| Lateral tibial cartilage volume (mm$^3$) | 2692 ±670 | 2544 ±668 | 0.104 |
| Medial femoral cartilage volume(mm$^3$) | 4679 ±1174 | 4354 ±1181 | 0.055 |
| Lateral femoral cartilage volume(mm$^3$) | **4859 ±1254** | **4437 ±1305** | **0.022** |
| Patellar cartilage volume (mm$^3$) | 3534 ±949 | 3421 ±1006 | 0.393 |
| Knee pain prevalence(%)* | **45%** | **20%** | **<0.001** |
| Total tibial bone area (mm$^2$)* | 3017 ±428 | 2934 ±498 | 0.191 |
| Patellar bone volume (mm$^3$) | 13970 ±3196 | 13770 ±3440 | 0.651 |
| Mean total cartilage defects score* | **4.4 ±1.3** | **4.0 ±1.2** | **0.039** |
| Mean leg strength (kg)* | 128 ±4.5 | 126 ±4.4 | 0.718 |
| Any bone marrow lesion[#^] | 68% | 60% | 0.249 |
| Any meniscal tear[@^] | 20% | 23% | 0.367 |

Where errors are shown, results are means ± SD
BMI (body mass index), ROA (radiographic osteoarthritis), JSN (Joint space narrowing)
Mean total cartilage defects score (mean of sums of medial tibial, medial femoral, lateral tibial and lateral femoral cartilage defects)
*significantly different between offspring and controls in the whole baseline study population (using conditional logistic regression)
[#]Any bone marrow lesion= tibial, femoral and/or patella
[@] Any meniscal tear=medial and/or lateral
[^]Measured at phase 2 (two years after the baseline visit)

**Table 5.3.** Comparison of radiographic changes and cartilage loss (absolute) between offspring and controls

| **Outcome factor** | **Offspring (N=115)** | **Controls (N=105)** | |
|---|---|---|---|
| **Radiographic score changes** | **Mean score ±SD** | **Mean score ±SD** | **P-Value** |
| Increase in medial JSN | **0.32 ±0.56** | **0.17 ±0.39** | **0.019** |
| Increase in lateral JSN | 0.07 ±0.35 | 0.09 ±0.32 | 0.774 |
| Increase in total JSN | 0.39 ±0.70 | 0.25 ±0.52 | 0.113 |
| Increase in total medial osteophytes | **0.35 ±0.78** | **0.15 ±0.41** | **0.025** |
| Increase in total lateral osteophytes | **0.42 ±0.92** | **0.18 ±0.46** | **0.018** |
| Increase in total osteophytes | **0.77 ±1.44** | **0.34 ±0.71** | **0.007** |
| Increase in total ROA score | **1.15 ±1.90** | **0.59 ±0.87** | **0.007** |
| **Cartilage loss (absolute)** | **Mean loss ($mm^3$) ±SD** | **Mean loss ($mm^3$) ±SD** | **P-Value** |
| Medial tibial | **-610 ±327** | **-518 ±347** | **0.047** |
| Lateral tibial | -300 ±370 | -297 ±412 | 0.953 |
| Medial femoral | -698 ±331 | -697 ±380 | 0.981 |
| Lateral femoral | -701 ±337 | -689 ±391 | 0.821 |
| Patellar | -778 ±633 | -777 ±643 | 0.992 |

Total = tibial + femoral

**Table 5.4.** Multivariable analyses of differences between offspring and controls in changes in radiographic changes and cartilage loss (absolute)

| Outcome factor | Unadjusted | Adjusted[a] | Adjusted[b] |
|---|---|---|---|
| **Radiographic changes** | **Difference in ratios and 95% confidence interval** | | |
| Increase in medial JSN | **+2.03 (+1.11, +3.51)** | **+2.04 (+1.12, +3.52)** | **+1.93 (+1.04,+3.51)** |
| Increase in lateral JSN | +0.82 (+0.31,+2.83) | +0.82 (+0.31,+2.83) | +0.53 (+0.21,+1.80) |
| Increase in total JSN | +1.50 (+0.91,+2.60) | +1.51 (+0.93,+2.53) | +1.44 (+0.82,+2.32) |
| Increase in total medial osteophytes | **+2.34 (+1.11,+4.53)** | **+2.32 (+1.11,+4.57)** | +1.84 (+0.93,+3.80) |
| Increase in total lateral osteophytes | **+2.32 (+1.22,+4.63)** | **+2.51 (+1.27,+5.11)** | +1.91 (+0.92,+3.93) |
| Increase in total osteophytes | **+2.30 (+1.30,+4.03)** | **+2.36 (+1.33,+4.24)** | +1.63 (+0.94,+2.92) |
| Increase in total ROA score | **+1.90 (+1.31,+3.04)** | **+1.81 (+1.21,+2.79)** | +1.52 (+0.93,+2.23) |
| **Cartilage loss (absolute)** | **Difference in means ($mm^3$) and 95% confidence interval** | | |
| Medial tibial | **-91.52 (-181.61,+1.31)** | -78.81 (-158.91,+1.23) | -79.13 (-161.92,+3.71) |
| Lateral tibial | -3.00 (-107.90,+101.78) | +10.62 (-90.59,+112.02) | +35.41 (-69.33,+140.12) |
| Medial femoral | -1.23 (-101.39,+98.72) | +30.87 (-56.11,+117.91) | +18.59 (-72.24,+109.41) |
| Lateral femoral | -11.80 (-114.42,+90.80) | +30.72 (-60.42,+121.72) | +45.81 (-45.43,+136.91) |
| Patellar | -0.90 (-171.57,+169.82) | +15.93 (-132.63,+164.54) | +80.20 (-67.33,+227.69) |

[a] Adjusted for age, sex and corresponding baseline measure
[b] Adjusted for [a] + baseline differences between offspring and controls (BMI, knee pain, cartilage defects score, tibial bone area and leg strength)
Total = tibial + femoral

There were no significant differences between the two groups for percentage per annum cartilage loss at any site. Medial tibial region showed a higher percentage per annum loss in the offspring group without reaching statistical significance in either the unadjusted [(dm = -0.31 (-0.72, +0.03; p = 0.078)] or the fully adjusted model [(dm = -0.30 (-0.71, +0.01; p = 0.055)].

## 5.4 Discussion

This is the first study to confirm that offspring of those with a knee replacement for OA have a higher risk of worsening knee OA over 10 years. Despite no difference in ROA (which had a low prevalence) at baseline between the offspring and controls, offspring experienced greater increases in medial JSN and osteophytes at all sites. Offspring also had higher absolute cartilage volume loss. The increases in osteophytes and cartilage volume loss were largely mediated by differences between the offspring and controls at baseline (BMI, knee pain, cartilage defects, bone size and leg strength) as the estimates were reduced by 18-30% for osteophytes and 14% for absolute cartilage volume loss. Increase in medial JSN was independent of these baseline differences and accounted for only 5% reduction in estimates.

Several studies have described the role of genetics in prevalent disease using radiographs [68, 153] but very few have examined the influence of genetic factors on disease over time and none have done so in a younger population. Results from this study not only suggest that offspring with a family history of knee OA are at a higher risk of worsening knee OA over 10 years but also highlight the structural and non-structural factors that mediate these changes. The data shows that OA is not very common at age 45 in those with a predisposition to OA but becomes more prevalent over a 10-year time frame compared to a control population. This suggests that the genes responsible may express themselves later in life, possibly through interaction with environmental factors such as BMI and muscle strength, as pointed out by reduction in estimates after adjustment for baseline differences. Another possibility is that the mechanisms counteracting the expression of these genes are more effective at a younger age.

The data from this study also suggests that progression of both JSN and osteophytes are under genetic influence. Previously only Zhai *et al.* [154] have shown high heritability estimates for disease progression in the medial compartment of the knee over 7 years using a twin study design. Our results are consistent with Zhai *et al.* for the progression of JSN only, as they did not find any significant heritability estimates for osteophytes. These results point to some interesting aspects of the role genes play in the progression of OA. Firstly, our data suggests that both JSN and osteophytes are under genetic influences as suggested by higher progression of JSN in offspring in the medial compartment and osteophytes at all sites.

Previously, Uitterlinden *et al.* [155], have shown that two separate genes control the expression of JSN and osteophytosis in a population-based sample of healthy older adults. Interestingly, progression of osteophytes was mediated by baseline differences between the two groups, whereas progression of medial JSN was independent of these differences. This suggests that the gene responsible for progression of osteophytes possibly interacts with environmental factors such as BMI and muscle strength to express its effect. The twin study design is often criticized due to the assumption of similar shared environment between monozygotic and dizygotic twins. Unlike twins, offspring and controls do not share the same environment, which would explain why consistently higher estimates for progression of osteophytes at all sites were observed.

Offspring also had a significantly higher absolute cartilage volume loss at medial tibial site compared to controls over 10 years. As mentioned previously, the gene coding for COL2A1 has been shown to be associated with JSN [155]. COL2A1 is a structural protein found in articular cartilage, which explains the similar trend shown by medial JSN and medial tibial cartilage loss. Also similar to JSN, we saw the association only in the medial compartment. The fact that we did not see any differences between the two groups for medial femoral cartilage volume loss, raises a few questions: (i) it is possible that cartilage volume loss at medial femoral and medial tibial sites are under separate genetic, structural or environment influences (ii) cartilage volume loss at the medial femoral site contributes less to JSN or happens later in life (iii) cartilage at these two sites varies in composition (iv) other co pathologies such as meniscal tears or BMLs might be associated more strongly with tibial compared to femoral cartilage volume loss (v) we used different methodologies to measure cartilage volume at the two sites, which might have led to measurement error.

Previous work from the offspring study has shown the role of genetics for the development of meniscal tears and BMLs. Ding *et al.* [94] showed that offspring had a significantly higher prevalence for meniscal tears, whereas Zhai *et al.* [106]showed high heritability estimates for both the prevalence and severity of BMLs in offspring group sibling pairs. Interestingly adjusting for medial meniscal tears did not alter the effect size of difference in ratio for change at medial JSN site, but adjusting for BMLs changed the effect size by more than 10%. Moreover, neither explained a majority of the change. It should be noted that both of these

structures were scored at the first follow up, two years after the baseline visit, as we only had the T1-weighted fat suppressed MRI sequences at baseline.

Baseline differences mediating the higher risk of ROA progression and cartilage volume loss is biologically plausible. High BMI is a known risk factor for both ROA progression and cartilage volume loss [156]. Tibial bone area, reduced leg strength and cartilage defects are not only risk factors for ROA progression [125, 157] but also had high heritability in sib-pair analysis from the present cohort [70]. Interpretation of higher prevalence of knee pain in the offspring is tricky as the assessment of knee pain is subjective and can be influenced by a variety of factors such as recall bias due to family history of OA. Nevertheless, there is evidence pointing to genetic contribution to expression of pain in knee OA. We have previously shown high heritability of knee pain in a sib-pair study [70]. Furthermore, polymorphisms in COMT and TRPV1 genes have been identified which could alter the processing of nociceptive pain associated with OA [43]. A high prevalence of knee pain in the offspring suggests that genetic factors may also lead to knee pain. However, adjustment for knee pain did not change the results in the present study. Different baseline characteristics in the offspring (including higher prevalence of MRI assessed structural abnormalities) could also mean that onset of the disease process in the offspring occurs at a younger age.

One of the major strengths of our study is the long follow-up period. This study has the longest follow-up period for any OA study using MRI. Another strength of this study is the exploration of the structural and non-structural factors mediating ROA changes and cartilage volume loss. However, this study has potential limitations as well. Over the ten years there was a loss to follow-up of around 40%. Such a high number, although not ideal, is expected in a long follow up period. Although we did not see any major differences in the main study variables between participants who were followed-up and who were lost to follow-up but it can still be a potential source of bias in the results shown in this study. Loss to follow-up also meant that the initial paired design of the study was invalidated. Loss of pairing resulted in a slight gender and age imbalance between offspring and controls. Nonetheless, all our analyses were adjusted for age and sex and adjusting for these had little effect on the results. Moreover, while we could adjust for meniscal tears and BMLs scored at 2 years we did not have them at baseline possibly leading to greater measurement error. Lastly, tibial and femoral cartilage volume were segmented using different methodology as was outlined in the

manuscript. Separate readers performed the measurements, which resulted in differences in how the scans were processed. Although both methods are almost equally sensitive at picking up any change in cartilage volume [158], this difference can still be a source of potential bias.

**Conclusion:**

The offspring of subjects having a total knee replacement have greater worsening of ROA (both JSN and osteophytes) and higher medial tibial cartilage volume loss over ten years. Most of these changes are mediated by differences in baseline characteristics of offspring and controls except for increase in medial JSN.

***Note:*** Letter to the editor by Kuijer *et al.* regarding results in this Chapter and our reply are attached in Appendix A.

# CHAPTER SIX

# The Clinical Significance, Natural History and Predictors of Bone Marrow Lesion Change Over Eight Years

# 6.1 Introduction

Osteoarthritis (OA) is the most common joint disorder worldwide, and the knee is the most common joint affected [159, 160]. Bone marrow lesions (BMLs) play a key role in the pathogenesis of knee OA – they are associated with OA symptoms such as pain and function, and predict cartilage loss and joint replacement surgery [91, 93, 161, 162]. In a recent Delphi exercise that aimed to establish a definition for OA on magnetic resonance imaging (MRI), BMLs were included as a key component of the diagnostic criteria [101].

The current literature on the natural history of BMLs is conflicting, with significant variation depending on the study population. A study in a healthy population has shown that incident BMLs developed in 14% of individuals over 2 years, and that knee pain was more likely to develop in these participants [163]. The same study showed that nearly one-half of the BMLs present at baseline completely resolved, while another study of middle-aged healthy women over 2 years found similar results [164]. Studies in symptomatic OA populations generally show a lower percentage of BMLs resolving, with one study reporting that less than 1% of patients showed a BML decrease over 30 months [165]. Other studies have quoted higher figures, with 10% of BMLs resolving over 2 years in a study by Kornaat and colleagues [166]. Our group has previously reported that rates of incident BMLs were low (7%), with about one-quarter of BMLs showing an increase or a decrease in size over 2.7 years in a population-based cohort of older adults with and without OA [93]. The reasons behind these variations are unclear; however, it is worth noting that no study has looked at the natural history of BMLs beyond 3 years.

Pain is a key criterion for a clinical diagnosis of OA. A number of studies have reported an association between BMLs and pain across a range of demographics and activities [167-171]. Furthermore, longitudinal studies have shown that increases in BML size and incident BMLs are both associated with increasing knee pain over 2 to 3 years [76, 172]. However, some studies have shown no association between BMLs and pain longitudinally [166, 173] or cross-sectionally [86].

Given the role of BMLs in OA, there has been interest in the risk factors that lead to an increased risk of developing BMLs. There is significant overlap with the major risk factors for OA, and age and weight have been shown to be some of the strongest risk factors for

BMLs [174, 175]. Physical activity, particularly doing over 10,000 steps per day, may aggravate existing BMLs [65]. Recently, vascular risk factors have also been implicated due to their effects on blood flow in the small vessels of subchondral bone [176]. Smoking, increased serum glucose levels, serum cholesterol and triglyceride, fatty acid intake, carbohydrate intake and changes in retinal microvasculature have all been associated with BMLs [177-181]. There is also a significant genetic component [106].

The conflicting data on natural history and clinical significance may be attributable to the differing methodology in many of these studies. These include differences in imaging protocols, sample size, age, sites measured, and severity of OA in the study sample. Importantly, few studies have followed the progression of BMLs beyond 3 years. The aims of this study were to describe the natural history of BMLs over 8 years, to examine the relationship between change in BML size and change in knee pain, and to examine factors predicting change in BML size.

## 6.2 Materials and methods

### 6.2.1 Study subjects

This study was conducted as part of the Offspring study, which is an ongoing population-based study. The Offspring study began in southern Tasmania (primarily in the capital city of Hobart) in June 2000. One-half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000 [102]. The diagnosis was confirmed by reference to the medical records of the orthopedic surgeon and the original radiograph when possible. Controls were age and sex matched and were randomly selected from the population. Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). This study includes data from the second and third visits at approximately 2 and 10 years respectively, because T2-weighted MRI scans were not performed at baseline.

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants.

### 6.2.2 Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$). Smoking was assessed by questionnaire and categorized as current smoker, past smoker or never smoked [109] . Physical activity was also assessed by a self-administered questionnaire that assessed the amount of time spent in light and strenuous physical activity on a five-point scale [182]. Participants were asked about the number of days during the last 14 days spent doing at least 20 minutes of strenuous exercise (that is, bicycling, brisk walking, jogging, aerobics, and so forth that was enough to raise your pulse rate or cause you to breathe faster) and light

exercise (that is, walking, light housework, slow bicycling, and so forth that was not severe enough to cause a pulse rate rising or breathing increase). The participants then chose a score between 1 and 5, where score 1 represents no days, score 2 represents 1 or 2 days, score 3 represents 3 or 5 days, score 4 represents 6 or 8 days, and score 5 represents 9 days or more of exercise.

### 6.2.3 Leg strength

Leg strength was measured by dynamometry at the lower limb, involving both legs simultaneously. This primarily involves the hip flexors and knee extensors. Each measure was performed twice, with instructions given prior to testing. The repeatability estimate (Cronbach's alpha) was 0.91. The device was calibrated by suspending known weights at regular intervals [150].

### 6.2.4 Knee pain

Knee pain was assessed by self-administered questionnaire using the Western Ontario and McMaster Universities Osteoarthritis Index at both visits [78]. Five categories of pain (walking on flat surface, going up or down stairs, at night, sitting or lying, and standing upright) were assessed separately with a 10-point scale from 0 (no pain) to 9 (most severe pain). Each score was then summed to create a total pain score (range 0 to 45).

### 6.2.5 Radiography

A standing anteroposterior semiflexed view of the right knee (at 15° flexion) was performed in all participants at baseline and 10 years. Radiographs were scored individually for osteophytes and joint space narrowing. Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial joint space narrowing, lateral joint space narrowing, medial osteophytes (femoral and tibial combined), and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers

simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International atlas [83]. A nonzero score in either joint space narrowing or osteophytosis was regarded as evidence of radiographic osteoarthritis (ROA). Reproducibility was assessed in 50 radiographs, 2 weeks apart, and yielded an intraclass correlation coefficient of 0.99 for osteophytes and 0.98 for joint space narrowing.

### 6.2.6 Magnetic resonance imaging

An MRI scan of the right knee was performed on a 1.5 T whole-body magnetic resonance unit (Picker, Cleveland, OH, USA) with the use of a commercial transmit–receive extremity coil. Knees were imaged in the sagittal plane and the following image sequences were used: visit two, a T2-weighted fat saturation two-dimensional fast spin echo (flip angle 90°; repetition time 3,067 ms; echo time 112 ms; field of view 16 cm; 256 × 256 matrix; slice thickness of 4 mm with a between-slices gap of 0.5 to 1.0 mm); and visit three, a T2-weighted fat saturation two-dimensional fast spin echo (flip angle 90°; repetition time 3,067 ms; echo time 112 ms; field of view 16 cm; 256 × 256 matrix; slice thickness of 2 mm with a between-slices gap of 0.5 mm).

Visit one only involved T1 MRI scans, which were not suitable for comparison of BMLs over time. Subchondral BMLs were assessed using Osirix software (University of Geneva, Geneva, Switzerland) and were defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella, and inferior patella sites as described previously [93]. One trained observer scored the BMLs by measuring the maximum area ($cm^2$) of the lesion at both time points. The observer manually selected the MRI slice with the greatest BML size. The BML with the largest size was recorded if more than one lesion was present at the same site. MRIs at both time points were read paired with the chronological order known to the observer but blinded to clinical status. Participants were given a BML score ($cm^2$) for each of the six sites (medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella, and inferior patella sites) as well as a total BML score, which was the sum of the scores at each site. Change in BML size was then calculated by subtracting the visit two BML size from the visit three BML size.

Intraobserver repeatability was assessed in 40 subjects with at least a 2-week interval between the readings. The intra-class correlation coefficient was 0.97.

To examine the natural history of BMLs, a significant change in BML size was defined as any change above or below the least significant criterion (LSC). The LSC takes into account measurement error and the correlation between BML measurements at baseline and follow-up. The formula is as follows, where $\sigma$ is the standard error of the mean and $\rho$ is the serial correlation:

$$LSC = 1.96 \times \sigma\sqrt{2(1-\rho)}$$

The LSC was calculated for each of the six sites in the knee (11 $mm^2$ for medial femoral, 17 $mm^2$ for lateral femoral, 16 $mm^2$ for medial tibial, 14 $mm^2$ for lateral tibial, 15 $mm^2$ for superior patellar, and 13 $mm^2$ for inferior patellar BMLs). This was then used to calculate the number of BMLs increasing and decreasing in size, where an increase in BML size was defined as any change greater than the LSC, and *vice versa* for a decrease in BML.

Meniscal damage was assessed by a trained observer on T1-weighted MRI scans as described previously [110]. Each meniscus is divided into three segments (anterior horn, body and posterior horn) for the assessment of both meniscal extrusions and tears.

Extrusion is defined as when meniscal tissue extends beyond the tibial margin, and complete extrusion is defined as when the meniscus has no contact with the joint space. For extrusions, each segment (anterior horn, body, and posterior horn) of both medial and lateral menisci were scored on a scale from 0 to 2 (0 = no extrusion, 1 = partial meniscal extrusion, 2 = complete meniscal extrusion with no contact with the joint space). Each meniscus can have a maximum score of 6 and a total knee score of 12 for extrusions.

A maximum score of 6 can be given for tears (0 = no damage, 1 = one of three meniscal areas involved (anterior, middle, and posterior horns), 2 = two of three areas involved, 3 = all three areas involved). This value was then scored for both medial and lateral menisci, giving a total score of 6.

These scores were summed to create a total meniscal pathology score, which had a possible range from 0 to 18.

### 6.2.7 Statistical analysis

The characteristics of study participants were compared using an independent-samples *t* test for continuous variables and a chi-squared test for categorical variables. Linear regression was used to estimate the relationship between change in pain and change in BML size. This was performed using total BML area (summed across all six sites) as well BML area at each site specifically. Multivariable analyses were adjusted for age, sex, BMI, leg strength, and the presence of ROA. Interactions between BML change and sex, and between BML change and offspring–control status, were assessed from the coefficient and its standard error of product terms was formed from the covariates for the study factors involved. Linear regression was also used to examine potential factors predicting a change in BML size. Univariable analysis was performed with a range of lifestyle and demographic factors (BMI, physical activity, smoking status, ROA, and offspring–control status) and those that were significantly associated were included in the multivariable model together with covariates for age and sex to adjust for these factors.

Standard diagnostic checks of model adequacy were performed on all final models. Residuals from all models were normally distributed, or approximately so, without evidence of heteroskedasticity.

Values of $P < 0.05$ were considered statistically significant. All statistical analysis was performed on Intercooled Stata 12.0 for Windows (StataCorp LP).

## 6.3 Results

### 6.3.1 Participant characteristics

The participants in this study were 198 subjects with complete MRI measures at the 2-year and 10-year visits (52.7% of those studied at baseline). There were no significant differences in sex, BMI, age, height, weight, frequency of ROA, and pain at baseline between those lost to follow up ($n = 178$) and the participants in our study ($n = 198$) (data not shown). Table 6.1 presents the characteristics of the study sample. BMLs were present in 64% (127/198) of the sample at visit two, with an average BML size of 0.63 $cm^2$. Of note, those with BMLs reported higher levels of pain at visit two and had a greater change in BML size. There were no significant differences in sex, age, BMI, offspring status, physical activity levels, height, weight, or change in pain, although those with BMLs tended to have a higher proportion with ROA compared with those with no BMLs. The mean (standard deviation) of physical activity in our cohort was 2.61 (1.33) for strenuous and 4.09 (1.11) for light activity respectively (data not shown).

### 6.3.2 Natural history

The 127 participants with a BML had a total of 229 BMLs present at visit two (58 had a BML at one site, 45 had a BML at two sites, 17 had a BML at three sites, five had a BML at four sites and two had a BML at five sites). Figure 6.1 describes the natural history of these BMLs. Roughly one-quarter of BMLs increased ($n = 55$) or decreased ($n = 49$) in size, whilst the remainder remained unchanged in size ($n = 125$) based on a change less than the LSC. Of those without BMLs at baseline ($n = 71$), slightly over one-half developed one or more incident BMLs ($n = 37$) over the 8 years. There was no significant difference in natural history between offspring and controls (data not shown).

**Table 6.1.** Participant characteristics

| | **BML present (*n* = 127)** | **BML not present (*n* = 71)** | ***P* value** |
|---|---|---|---|
| Females (%) | 41% (51/127) | 47% (33/71) | 0.4 |
| Age (years) | 47.6 (6.5) | 47.2 (6.0) | 0.65 |
| Offspring (%) | 58% (74/127) | 49% (35/71) | 0.22 |
| BMI (kg/m$^2$) | 28.0 (5.8) | 27.0 (4.2) | 0.24 |
| Height (cm) | 168.5 (9.2) | 169.1 (8.9) | 0.7 |
| Weight (kg) | 79.6 (18.1) | 77.6 (15.1) | 0.43 |
| Leg strength (kg) | 114.9 (47.4) | 118.3 (44.3) | 0.64 |
| Active smokers (%) | 17.3 | 15.5 | 0.77 |
| Light activity (per unit change) | 4.1 (0.09) | 4.00 (0.15) | 0.43 |
| Strenuous activity (per unit change) | 2.65 (0.12) | 2.52 (0.15) | 0.51 |
| Radiographic osteoarthritis (%) | 20% (26/127) | 10 (7/71) | 0.06 |
| Pain score (0 to 29) | **3.7 (5.9)** | **1.3 (3.1)** | **<0.01** |
| Change in pain score (-25 to 44) | 2.5 (8.1) | 2.2 (4.2) | 0.84 |
| Total BML area (0 to 4.10 cm$^2$) | **0.63 (0.80)** | – | – |
| MF BML area (0 to 1.98 cm$^2$) | **0.37 (0.50)** | – | – |
| LF BML area (0 to 2.54 cm$^2$) | **0.64 (0.75)** | – | – |
| MT BML area (0 to 1.83 cm$^2$) | **0.33 (0.36)** | – | – |
| LT BML area (0 to 1.99 cm$^2$) | **0.26 (0.31)** | – | – |
| SP BML area (0 to 1.70 cm$^2$) | **0.38 (0.34)** | – | – |
| IP BML area (0 to 1.06 cm$^2$) | **0.23 (0.27)** | – | – |
| Change in BML area (-2.09 to 4.46 cm$^2$) | **0.61 (1.03)** | **0.28 (0.46)** | **0.01** |

Values were taken from visit two of the study, except for radiographic osteoarthritis that was taken from visit one. Change refers to the difference in values between visit two and visit three. Values represent mean (standard deviation) unless percentages. Light and strenuous activity were rated on a five-point scale: 1 = no days, 2 = 1 or 2 days, 3 = 3 to 5 days, 4 = 6 to 8 days, and 5 = 9 days or more spent doing at least 20 minutes of the respective level of activity in the past 14 days. BMI, body mass index; BML, bone marrow lesion; IP, inferior patella; LF, lateral femoral; LT, lateral tibial; MF, medial femoral; MT, medial tibial; SP, superior patella. Bold data indicate $P$ <0.05.

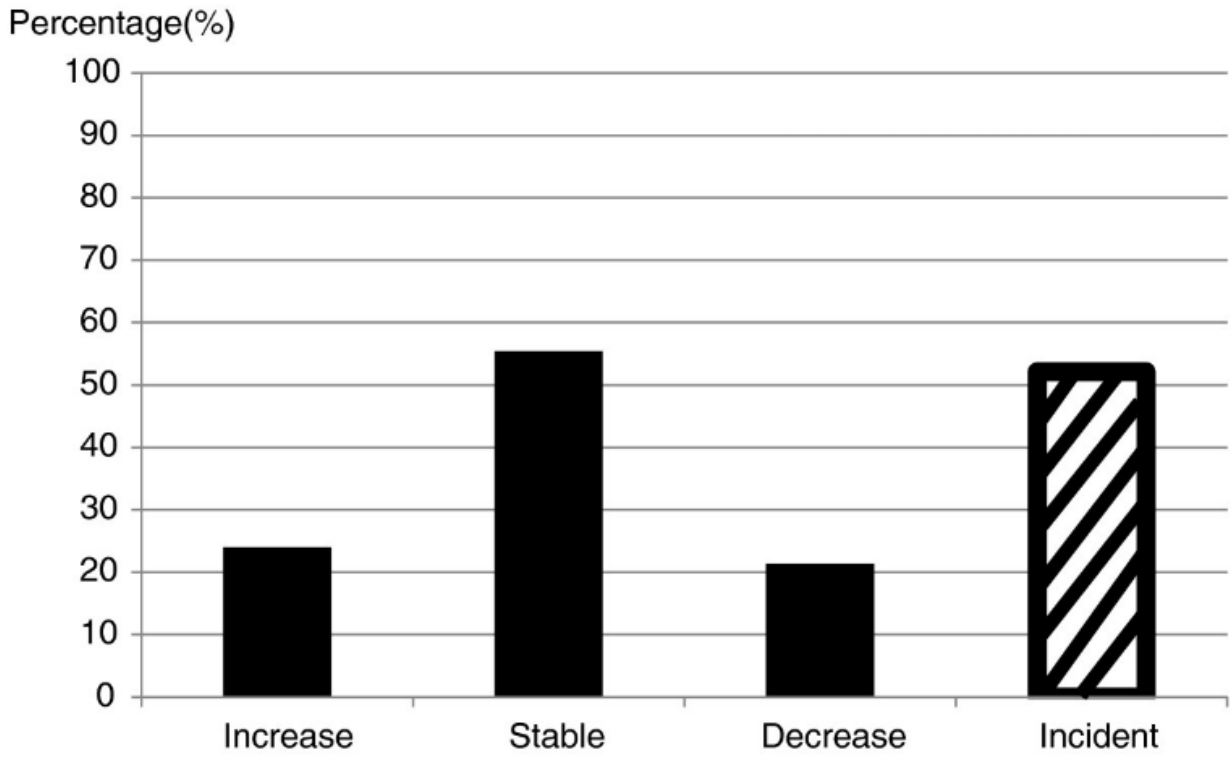


**Figure 6.1.** Natural history of bone marrow lesions

### 6.3.3 Pain

Table 6.2 presents associations between change in total BML size and change in pain. Every 1 $cm^2$ increase in BML size resulted in a 1.53 (95% confidence interval = 0.37, 2.70) unit increase in pain score after adjustment for age, sex, BMI, leg strength, and the presence of ROA. Adjusting for baseline joint space narrowing, osteophytes, meniscal extrusion, and meniscal tears did not significantly affect our findings (<10% change in the beta coefficient following further adjustment). A significant offspring–control interaction was present ($P = 0.08$), with change in BML size more strongly associated with change in pain among offspring than controls. Furthermore, this association was stronger in males compared with females among both the offspring group and the whole sample.

Table 6.3 presents associations between site-specific change in BML size and change in pain. Changes in medial and lateral tibial BMLs were significantly associated with change in pain, with the association stronger among offspring at the medial tibial site (*P* value for interaction was <0.01). After adjustment for age, sex, BMI, leg strength, and ROA, change in lateral tibial BMLs and change in pain was no longer significantly associated. No significant association was found between change in BML size and change in pain at other sites.

For those with no pain or BMLs present at baseline ($n = 42$), the development of a BML was significantly associated with an increase in pain after adjustment for age, sex, BMI, leg strength, and ROA in offspring and controls combined with a change in pain score of 3.60 (95% confidence interval = 1.14 to 6.05) points per 1 $cm^2$ change in BML size (not shown in Table 6.3).

### 6.3.4 Factors affecting bone marrow lesion change

Table 6.4 presents predictors of BML change. BMI and strenuous activity were deleteriously associated with change in BML size. These associations remained statistically significant after adjusting for age and sex and each other. Smoking status, the presence of ROA, light activity, offspring–control status, and leg strength was not associated with change in BML size.

**Table 6.2.** Relationship between change in WOMAC and change in BML size

| | Univariable | Multivariable[a] | Females[a] | Males[a] |
|---|---|---|---|---|
| Total | **1.74 (0.65, 2.84)** | **1.53 (0.37, 2.70)** | 0.63 (-0.93, 2.20) | **2.53 (0.76, 4.30)** |
| Offspring | **2.68 (1.22, 4.13)** | **2.50 (0.96, 4.05)** | **2.25 (0.10, 4.41)** | **3.06 (0.88, 5.24)** |
| Controls | -0.05 (-1.72, 1.62) | -0.39 (-2.23, 1.44) | -0.77 (-3.51, 1.98) | 1.44 (-1.25, 4.14) |

Data presented as beta coefficient (95% confidence interval). Values are the change in WOMAC pain score per $cm^2$ change in BML size. An interaction between offspring–control status and change in BML size ($P = 0.01$) as well as sex and change in BML size ($P = 0.08$) on change in pain was present. BML, bone marrow lesion; WOMAC, Western Ontario and McMasters Universities Arthritis Index. Bold data indicate $P < 0.05$. [a]Adjusted for age, sex, body mass index, leg strength, and radiographic osteoarthritis.

**Table 6.3.** Relationship between change in WOMAC and site-specific change in BML size

| | Univariable | Multivariable[a] |
|---|---|---|
| Medial tibial | **2.96 (0.59, 5.34)** | **3.67 (0.89, 6.45)** |
| Controls | -1.39 (-4.18, 1.40) | -3.38 (-7.15, 0.39) |
| Offspring | **8.99 (5.30, 12.68)** | **8.98 (5.22, 12.73)** |
| Lateral tibial | **2.37 (0.08, 4.66)** | 1.98 (-0.36, 4.32) |
| Medial femoral | 2.11 (-1.14,5.36) | 1.63 (-1.64, 4.90) |
| Lateral femoral | -0.09 (-2.41, 2.24) | -0.69 (-3.11, 1.73) |
| Superior patella | 0.74 (-2.73, 4.21) | 0.61 (-2.85, 4.08) |
| Inferior patella | 3.95 (-0.59, 8.50) | 4.30 (-0.26, 8.86) |

Data presented as beta coefficient (95% confidence interval). Values are the change in WOMAC pain score per $cm^2$ change in BML size. An interaction between offspring and control status was present at the medial tibial site ($P < 0.01$). BML, bone marrow lesion; WOMAC, Western Ontario and McMasters Universities Arthritis Index. Bold data indicate $P < 0.05$. [a]Adjusted for age, sex, body mass index, leg strength, and radiographic osteoarthritis.

**Table 6.4.** Predictors of change in bone marrow lesion size

| | Univariable | Multivariable[a] |
|---|---|---|
| mass index (kg/m$^2$) | **0.03 (0.00, 0.05)** | **0.03 (0.01, 0.05)** |
| Strenuous activity (per unit change) | **0.13 (0.03, 0.22)** | **0.14 (0.04, 0.23)** |
| Current smoker (yes/no) | 0.04 (-0.13, 0.20) | – |
| Ever smoker (yes/no) | 0.06 (-0.20, 0.31) | – |
| Radiographic osteoarthritis (yes/no) | 0.28 (-0.06, 0.61) | – |
| Light activity (per unit change) | 0.02 (-0.10, 0.13) | – |
| Offspring status (yes/no) | 0.13 (-0.11, 0.38) | – |
| Leg strength (kg) | 0.00 (0.00, 0.00) | |

Data presented as beta coefficient (95% confidence interval). Values are the change in bone marrow lesion size (cm$^2$) per unit change in covariates. All factors are from visit two, except for radiographic osteoarthritis that was collected at visit one. Strenuous and light activity were assessed on a five-point scale: 1 = no days, 2 = 1 or 2 days, 3 = 3 to 5 days, 4 = 6 to 8 days and 5 = 9 days or more. Bold data indicate $P$ <0.05. [a]Adjusted for age, sex, body mass index, and strenuous activity.

## 6.4 Discussion

This population-based study of middle-aged adults has investigated the natural history of BMLs over 8 years and the association between change in BML size and change in pain. Incident BMLs were common; roughly one-half of those without BMLs at visit two developed new BMLs by visit three. Of the BMLs present at visit two, 55% remained stable while 24% increased and 21% decreased in size. An increase in BML size or new BML resulted in a significant increase in knee pain, especially for male offspring. BMI and strenuous activity independently predicted change in BML size.

This is the first study to report the natural history of BMLs over an extended period of time. Many of the previous studies have been conducted over a much shorter timeframe. Davies-Tuck and colleagues reported a much higher proportion of BMLs improving, with 46% of BMLs resolving completely in a healthy, pain-free population over 2 years [163]. In a symptomatic population with ROA, less than 1% of BMLs resolved or reduced in size [165]. The conflicting data may be a reflection of different study populations as well as different grading systems used for the assessment of BMLs. In this study, patellar BMLs were also assessed, which may explain the high percentage of participants with BMLs compared with other studies that did not assess patella BMLs [93, 163, 164]. A previous study by our group in a population-based sample of older adults that employed the same quantitative BML methodology found very similar results to our current study where approximately one-quarter of BMLs both increased and decreased in size [93].

In our study, incident BMLs in subjects without BMLs at visit two were also high, most probably due to the period of follow-up. Other studies have reported much lower figures, ranging from 9 to 14% in a healthy population over 2 years [163, 164] and 20% in a cohort with symptomatic knee OA over 30 months [165]. Of clinical importance, the development of an incident BML was significantly associated with the development of pain in those who were pain free at visit two. This association has been corroborated by a prior study looking at healthy populations [163] and a cohort consisting of subjects with OA or at high risk of OA [76]. This observation further lends weight to the argument that BML development may be a major contributor to incident knee pain.

A 1 $cm^2$ increase in BML size resulted in a 2.5 unit increase in knee pain in those with a family history of OA, whereas no association was seen in controls. Previous findings from this cohort have shown that offspring with a family history of knee replacement were more likely to have a greater BMI, more knee pain, and less muscle strength cross-sectionally compared with matched controls [102]. However, there have been few studies examining the genetic factors influencing BMLs. Zhai and colleagues reported that BMLs have a significant genetic component in this cohort [106], but they did not investigate whether there was a genetic component to the role that BMLs play in pain. BMLs are perhaps more likely to cause pain in genetically susceptible individuals given that genes can discriminate those with OA and pain from those with OA without pain [183]. Alternatively, BML pathology may be different in those with a family history of OA and MRI is somewhat nonspecific with regard to the underlying pathology.

The association between change in BMLs and change in pain was also stronger in males compared with females. Few studies have reported on sex difference in BMLs. Davies-Tuck and colleagues reported that sex was not associated with the presence, development or persistence of BMLs [163], whilst Dore and colleagues found that males were more likely to have BMLs and have a BML increase over time [93]. In our cohort, males had significantly larger BMLs at both visit two and visit three. When we adjusted our model for BML size at visit two and visit three, however, the sex difference persisted, suggesting that there may be a difference in the way BMLs mediate pain between sexes.

When we examined site-specific BMLs and their association with pain, we found that tibial BMLs were associated with change in pain but not patellar or femoral BMLs. In particular, medial tibial BMLs were strongly associated with change in pain for offspring. To the best of our knowledge, no study has looked at site-specific associations between BMLs and pain. Studies have shown that BMLs can lead to increased bone mineral density locally [168, 184] and greater cartilage loss at the same site [162]. A local effect would thus be consistent with the existing literature.

Higher BMI and strenuous activity were found to predict BML change. Obesity is a strong risk factor for OA [49], and prior studies have also reported a cross-sectional association between BMI and BML prevalence and severity [185]. However, a 36-month follow-up

found no association between BML progression and BMI [185]. Similarly, high-intensity physical activity has been shown to increase the risk of OA [186, 187]. However these findings need to be balanced against the strong evidence demonstrating that physical activity improves symptoms and physical function in OA [188]. A recent longitudinal study by our group reported that physical activity measured by steps per day was deleteriously associated with BML change [65]. Whilst we found a significant association between strenuous physical activity and BML change, we did not find an association between light physical activity and BML change, suggesting intensity of activity may be important. Therefore, whilst physical activity may be good for symptoms, excessive physical activity may be detrimental to knee structure. Randomized controlled trials evaluating the effect of physical activity on a sensitive measure of knee structure, such as MRI, are needed to gain a better understanding of this relationship.

Our study has several potential limitations. Firstly, slightly different MRI protocols were used at visit two and visit three. Due to the long follow-up period, the protocol at visit three had slightly different parameters – namely a smaller slice thickness. This means that a greater number of small BMLs might have been picked up at visit three; the rate of incident BMLs over 8 years may therefore not be as high as our study indicates. There may also have been an overestimate of BML change, which would mean that the true magnitude of the association between BML change and change in pain is stronger.

Secondly, due to the long follow-up period, a significant proportion of our subjects were lost to follow-up. However, there were no significant differences in pain scores and demographics between those lost to follow-up and participants in this study, suggesting this bias was not systematic.

Thirdly, BML area was measured by taking the slice with the greatest BML size at a particular site. This is a surrogate measure of volume and may overestimate shallow, flat lesions. However, this method of BML measurement has proven to be sensitive to change in a recent clinical trial [189].

Fourthly, the interslice gap was 0.5 to 1.0 mm, which means that small BMLs might have been missed if they lay completely within the interslice gap, which seems unlikely.

Fifthly, we used a subjective measure of physical activity to assess the amount of light and strenuous activity that participants undertook. We also did not differentiate between different modes of physical activity such as weight-bearing and nonweight-bearing exercise, and did not specifically ask about strenuous incidental physical activity (for example, occupational or household activity). It is also important to note that only current physical activity data were captured over a 14-day period as opposed to a longitudinal measure of physical activity. However, the significant correlation between strenuous activity and BML change is consistent with pedometer-derived physical activity.

Sixthly, we did not assess analgesia such as paracetamol or nonsteroidal anti-inflammatory drugs or knee malalignment, which could have been potential confounders.

Lastly, ROA was assessed at baseline and not at visit two. This difference in timing may result in a slight underestimate in the prevalence of ROA at visit two, which may influence the borderline results.

**Conclusion**

In this midlife cohort, the proportion of BMLs increasing in size was similar to those decreasing in size, with the majority remaining stable. Change in BMLs can be predicted by lifestyle factors, namely BMI and strenuous activity. An increase in BML size or a new BML resulted in an increase in pain especially in males and those with a family history of OA.

# CHAPTER SEVEN

## Natural History and Clinical significance of Meniscal Tears over 8 Years in a Mid-Life Cohort

## 7.1 Background

Loss of meniscal function due to tears is a potent risk factor for knee osteoarthritis (OA) and may be one of the earliest changes in the OA causal pathway [24]. Meniscal tears share common risk factors with knee OA [94, 142] and explain more of the variation in joint space narrowing (JSN) than cartilage volume [190]. Cross-sectional studies using magnetic resonance imaging (MRI) have also shown that damage to menisci in the form of tears is paralleled by other structural abnormalities such as lower cartilage volume [94] and an increased severity of cartilage defects [94] and bone marrow lesions (BMLs) [191].

Although meniscal tears are a common finding in people with asymptomatic disease [192], it is a potential source of pain associated with OA. The periphery of menisci have nociceptive innervation [193, 194] and it is reasonable to hypothesise that meniscal tears that extend to this area can cause pain. However longitudinal studies, conducted over 15-24 months, have shown conflicting results thus far [75, 195]. It is uncertain if change in meniscal tears is directly associated with worsening pain [195] or if both meniscal damage and pain are a result of OA through intermediate pathologies (such as BMLs and effusion) rather than a direct link between the two [75].

Furthermore, there is limited longitudinal data on the natural history of meniscal tears. It is not clear how meniscal tears change over a long period of time and how change in meniscal tears is associated with global knee structural changes. The aim of this study was to describe the natural history of meniscal tears over 8 years, the predictors of change in meniscal tears and the association between change in meniscal tears and change in knee pain and structures.

## 7.2 Methods

This study was conducted as part of the Offspring study, a population-based study that began in Southern Tasmania in June 2000. Matched sampling was used to recruit the study participants (mean-age 47 (28–63) years; 57% females). Half of the participants were the adult offspring of patients (only one parent) who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000 [102]. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeons and the original radiographs when possible. The other half were age and sex matched controls, randomly selected from the population with no history of knee OA in either parent. This study includes data from the first (visit-2) and second (visit-3) follow-up visits at approximately two and ten years respectively, as we did not have the correct MRI sequence to score meniscal tears at baseline.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants.

Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). Participants were also excluded if they had undergone a knee replacement surgery or did so after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

### 7.2.1 Knee pain

Knee pain was assessed by self-administered questionnaire using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at both visits [93]. Five categories of pain (walking on flat surface, going up or down stairs, at night, sitting or lying, and standing upright) were assessed separately with a 10-point scale from 0 (no pain) to 10 (most severe pain). Each category was summed to create a total pain score (range 0 to 50). Furthermore, the five categories were clinically categorized into weight-bearing pain (including walking on

flat surface, going up or down stairs and standing) and non-weight-bearing pain (including pain at night and sitting or lying).

### 7.2.2 Knee joint injury

History of knee joint injury was assessed using a self-administered questionnaire [196] which included the following questions:

- "Have you ever had a previous knee injury which resulted in non-weight bearing treatment for 24 hours or more?"
- "If yes, then which knee?"
- "Please provide further details about the injury"

### 7.2.3 Magnetic resonance imaging

MRI of the right knee was performed as described previously [89, 104]. Knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Picker International, USA) using a commercial transmit-receive extremity coil. The following image sequence was used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 msec, echo time 12 msec, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an interslice-gap; and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256×256 matrix, slice thickness of 4 mm with an interslice gap of 0.5–1.0 mm.

### 7.2.4 Meniscal tears

Meniscal tears were assessed by a trained observer (musculoskeletal radiologist with several years of experience) on T2-weighted fat saturated (side by side) MR images at visit-2 and 3 of the study as previously described [110]. The proportion of the menisci affected by a tear was scored separately (0-2 scale; 0=absence of a tear, 1=simple tear of different types: longitudinal, oblique, radial or horizontal, 2=macerated tear signifying loss>50% area of

meniscal tissue) at the anterior, middle, and posterior horns. Anterior, middle and posterior scores were summed to create medial and lateral meniscal tear scores. The intra- and inter-observer correlation coefficient (expressed as intraclass correlation coefficient (ICC)) ranged from 0.86- 0.96 [111].

### 7.2.5 Meniscal extrusion

The extent of meniscal extrusion on the medial or lateral edges of the tibial femoral joint space, not including the osteophytes, was evaluated at visit-2 and 3 for the anterior, body, and posterior horns of the menisci on T1-weighted gradient echo MR images, as previously described [111]. A score from 0 to 2 was used (0 = no extrusion, 1 = partial meniscal extrusion, and 2 = complete meniscal extrusion with no contact with the joint space). The scores of anterior, body and posterior horns of medial or lateral menisci were summed to create a total meniscal extrusion score for each of the medial and lateral tibiofemoral compartments which had a possible range from 0 to 6. The intra- and inter-observer correlation coefficient ranged from 0.85 to 0.92 for meniscal extrusion [110]. All knees were evaluated for the presence of meniscal extrusion regardless of whether they had a meniscal tear or not.

### 7.2.6 Cartilage volume

Tibial and femoral cartilage volume was assessed on T1-weighted gradient echo MR images using Osiris (University of Geneva, Switzerland) and Cartiscope (ArthroLab, Montreal, Canada) software respectively at visit-2 and 3, as previously described [104, 111]. The coefficient of variation (CV) for intra-observer repeatability ranged from 2.0–2.2% for both tibial and femoral cartilage volume measurements [84, 130]. Total cartilage volume was calculated as: tibial + femoral cartilage volume.

### 7.2.7 Cartilage defects

Cartilage defects were assessed on T1-weighted gradient echo MR images on a 0-4 scale (0=normal; 1=focal blistering/signal changes; 2=<50% thickness loss; 3=>50% thickness loss; 4=full thickness defect) at visit-2 and 3, as previously described [113]. Intraobserver reliability ranged from ICC of 0.89-0.90 [113]. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.85-0.90 [113].

### 7.2.8 Bone marrow lesions

BMLs were assessed on T2-weighted fat saturated MR images at visit-2 and 3 and were defined as areas of increased signal adjacent to the subchondral bone [93]. One trained observer scored the BMLs by measuring the maximum area of the lesion in a specific compartment. The observer manually selected the MRI slice with the greatest BML size. The BML with the highest score was used if more than one lesion was present at the same site. The ICC for intra-observer reliability, assessed on 40 MR images, was 0.97.

### 7.2.9 Effusion

Effusion was assessed in the supra-patellar pouch on T2-weighted fat saturated MR images at visit-2 and 3 on a 0-3 scale [114]. Grade-0 signified absence of fluid over the upper margin of the patella in a sagittal image; Grade-1 signified some fluid above the upper margin of the patella but the length of the fluid column shorter than that of the patella; Grade-2 signified a fluid column above the upper margin of patella longer than the length of the patella; Grade-3 signified a fluid column above the upper margin of patella longer than the length of the patella with a thickness of $\geq$ 1cm. Intra-observer reliability was assessed in 50 MR images and yielded an ICC of 0.89-0.98. Pathological effusion was defined as any effusion score $\geq$2.

### 7.2.10 Radiography

A standing anteroposterior semiflexed view of the right knee (at 15° flexion) was performed in all participants at baseline and 10 years. Radiographs were scored individually for

osteophytes and joint space narrowing, as described previously [84]. Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial joint space narrowing (JSN), lateral JSN, medial osteophytes (femoral and tibial combined) and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International (OARSI) atlas [82]. A non-zero score in either joint space narrowing or osteophytosis was regarded as evidence of radiographic osteoarthritis (ROA). Reproducibility was assessed in 50 radiographs, two weeks apart, and yielded an ICC of 0.99 for osteophytes and 0.98 for JSN.

Readers for all the scans were either musculoskeletal radiologists with several years of experience in OA research or health professionals trained by musculoskeletal radiologists. Readers were not blinded to the chronological sequence of the radiographs and MRI scans.

### 7.2.11 Statistical analysis

Change in all MRI structures and leg strength was calculated as: Visit-3 score – Visit-2 score
T-test and Chi-square tests were used to describe the baseline characteristics of the participants with or without any change in mean meniscal tear score. T-test was further used to compare change in meniscal score between offspring and control groups. Poisson regression analysis was used to examine the predictors of change in meniscal tears and the association between change in meniscal tears and change in meniscal extrusion. Linear regression analysis was used to describe the association between change in meniscal tears and change in pain, cartilage volume loss and change in BMLs. Multivariable analyses were adjusted for demographics, body mass index (BMI), offspring-control status and knee structures (global knee structural factors known to be associated with the presence of meniscal tears or knee pain). Further analysis was performed to explore any offspring-control interaction in the multivariable models for all the above mentioned associations.

A P-value of less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 12.0 for windows (StataCorp LP).

## 7.3 Results

A total of 198 subjects (57% female, mean age 47 years) had complete MRI measures at visit-2 and 3. There were no significant differences in baseline characteristics between those lost to follow-up (n=133) and the participants in our study in terms of age, sex, BMI and ROA (data not shown).

### 7.3.1 Natural History

Figure 7.1A describes the prevalence of meniscal tears at visit-2. 22% of the participants (44/198) had at least one meniscal tear at any site. 41/44 participants had at least one meniscal tear at any of the three meniscal sites (anterior, body or posterior) in the medial compartment, whereas only 3 participants had at least one meniscal tear in the lateral compartment. None of the participants had a meniscal tear in both compartments.

41 participants with medial meniscal tears had 55 meniscal tears in total at all sites. 29/41 participants had a single meniscal tear at any site (anterior, body or posterior), 10/41 participants had a meniscal tear at 2 sites and 2/41 participants had a meniscal tear at all 3 sites. Medial posterior was the most commonly affected site (27/55), followed by medial body (21/55) and medial anterior sites (7/55) (Figure 7.1B). 37/55 meniscal tears were simple tears, whereas 18/55 were macerated tears.

3 participants with lateral meniscal tears had 8 meniscal tears in total at all sites. 1/3 participant had a meniscal tear at 2 sites and 2/3 participants had meniscal tears at all 3 sites. Lateral posterior was the most commonly affected site (4/8), followed by lateral body (3/8) and lateral anterior sites (1/8) (Figure 7.1B). 5/8 meniscal tears were simple tears, whereas 3/8 were macerated tears.

The majority of participant's menisci (84%) remained stable over 8 years. 16% of the participants (31/198) showed an increase in mean meniscal score – including incident tears (14/31) and increase in the severity of existing tears (17/31). Most of these changes affected the medial meniscus (87% (27/31)).

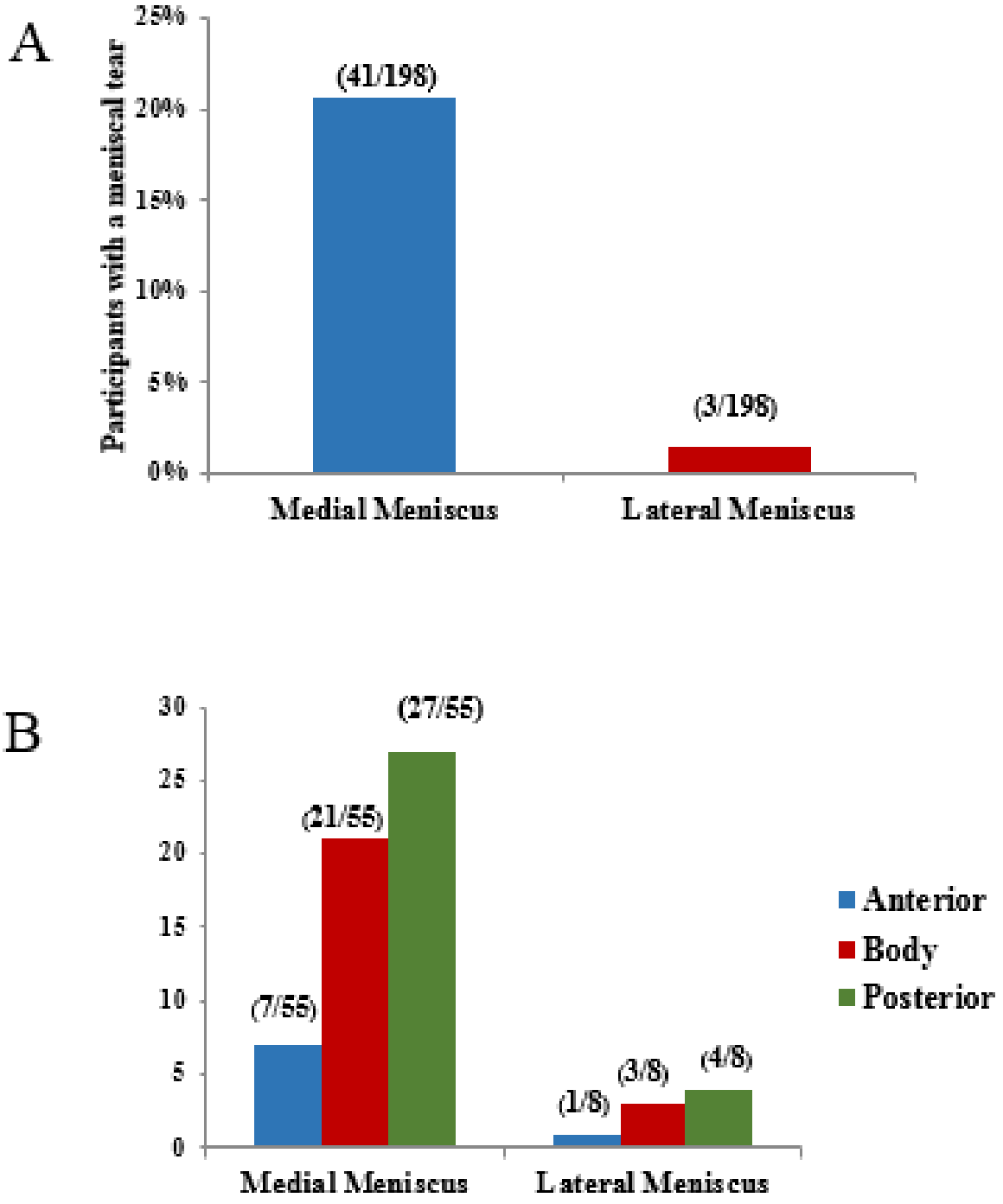


**Figure 7.1.** Prevalence and natural history of meniscal tears. **A)** Prevalence of meniscal tears at visit 2, **B)** Site-specific distribution of meniscal tears at visit 2

Most of the participants showed an increase at the posterior meniscal site (15/31), followed by body (12/31) and anterior (4/31) sites. None of the participants with a meniscal tear at visit-2 showed an improvement in meniscal tear score over 8 years.

Table 7.1 describes the (visit-2) characteristics of participants with and without any increase in mean meniscal tear score over 8 years. Participants with any increase in mean meniscal score were significantly older, heavier, had a higher percentage of offspring, prevalence of ROA, total femoral cartilage volume, total mean cartilage defect score, tibial bone area and prevalence of supra-patellar effusion compared to participants without any increase in mean meniscal score. Participants with any increase in mean meniscal tear score also had a higher percentage of male participants, worse pain score and a higher prevalence of BMLs but these differences did not reach statistical significance.

The majority of meniscal tear change occurred in the offspring group and this was significant at the total medial, total posterior and the total knee sites in comparison to the control group (all $p<0.05$).

**Table 7.1.** Characteristics (at visit-2) of participants with and without any change (incident tears and increase in score) in tears over 8 years

| | Any change (n= 31) | No change (n= 167) | p-value |
|---|---|---|---|
| Age (years) | **50.06 ± 6.35** | **47.37 ± 6.49** | **0.046** |
| Male (%)* | 57 | 39 | 0.069 |
| BMI (kg/m$^2$) | **29.51 ± 7.10** | **26.77 ± 4.38** | **0.008** |
| Offspring (%)* | **72** | **45** | **0.008** |
| Any ROA (%)*^ | **33** | **18** | **0.046** |
| WOMAC pain (mean) | 4.77 ± 7.14 | 2.63 ± 4.71 | 0.051 |
| Total tibial cartilage vol (mm$^3$) | 4868.43 ± 1012.85 | 4500.62 ± 1062.66 | 0.093 |
| Total femoral cartilage vol (mm$^3$) | **9562.64 ± 2377.24** | **8531.51 ± 2269.82** | **0.047** |
| Total cartilage defects (mean) | **5.24 ± 2.04** | **3.80 ± 1.43** | **<0.001** |
| Total tibial bone area (mm$^2$) | **3273.17 ± 473.89** | **3079.38 ± 473.01** | **0.049** |
| Any bone marrow lesion (%)* | 59 | 50 | 0.380 |
| Any pathological effusion (%)* | **55** | **34** | **0.028** |

Mean ± standard deviation except for percentages; *Determined by Chi square test, others by t-test
^Assessed at the baseline visit; the rest assessed at visit-2
Bold font denotes statistically significant (p=<0.05) results

## 7.3.2 Predictors of change

Table 7.2 describes predictors of change in total knee meniscal tears over 8 years. Age at visit-2, BMI, history of knee injury, cartilage defects, BMLs, JSN and osteophytes significantly predicted change in meniscal tears in unadjusted analysis. Only BMI and osteophytes independently predicted change in meniscal tears in the fully adjusted model. BMI showed a significant association in all compartments including anterior, body and posterior meniscal sub-groups whereas osteophytes predicted change in only total anterior and posterior tears (data not shown).

**Table 7.2.** Predictors of change in total knee meniscal tears over 8 years

| | Change in total knee meniscal tears over 8 years | |
|---|---|---|
| | Unadjusted<br>Risk ratio (95%CI) | Adjusted[a]<br>Risk ratio (95%CI) |
| Age | **1.06**<br>**(1.02, 1.11)** | 1.05<br>(0.98, 1.21) |
| BMI | **1.09**<br>**(1.03, 1.15)** | **1.11**<br>**(1.04, 1.17)** |
| Knee Injury | **2.16**<br>**(1.08, 6.01)** | 1.91<br>(0.93, 3.92) |
| Cartilage defects | **1.26**<br>**(1.05, 1.52)** | 0.77<br>(0.54, 1.09) |
| BMLs | **1.57**<br>**(1.06, 2.32)** | 0.87<br>(0.33, 2.29) |
| JSN | **3.17**<br>**(1.41, 7.16)** | 2.11<br>(0.74, 6.03) |
| Osteophytes | **1.79**<br>**(1.29, 2.47)** | **1.78**<br>**(1.17, 2.71)** |

a= adjusted for age/BMI/knee injury, offspring-control status, cartilage defects at visit-2, BMLs at visit-2 and/or ROA at visit-1.
Bold font denotes statistically significant (p=<0.05) results
**(No significant offspring-control interaction for any of the above mentioned associations)**

## 7.3.3 Pain

30/44 participants who had a meniscal tear reported knee pain at baseline.

Table 7.3 describes the association between change in meniscal tears and change in pain over 8 years. Increases in total knee meniscal tears was independently associated with increases in

total knee pain, pain on each individual WOMAC sub-scale and in weight bearing and non-weight bearing pain over 8 years in the whole population. There was also a significant offspring-control interaction at all sites with offspring showing significantly greater increases in pain per unit increase in meniscal tears compared to controls.

**Table 7.3.** Association between change in meniscal tears and change in pain over 8 years

| | **Change in pain over 8 years** | |
|---|---|---|
| Change in total knee meniscal tears | Unadjusted β (95%CI) | Adjusted[a] β (95%CI) |
| Whole group | **+2.87 (+1.84, +3.90)** | **+2.81 (+1.40, +4.22)** |
| -- Offspring | **+3.73 (+2.56, +4.89)** | **+2.84 (+1.22,+4.46)** |
| -- Controls | -0.48 (-2.72, +1.75) | -0.92 (-4.20, +2.36) |
| | **Change in pain subscales over 8 years** | |
| | Change in pain while lying in bed | |
| Whole group | **+0.89 (+0.64, +1.14)** | **+0.82 (+0.46, +1.18)** |
| | Change in pain while sitting | |
| Whole group | **+0.45 (+0.22, +0.67)** | **+0.35 (+0.04, +0.67)** |
| | Change in pain while standing | |
| Whole group | **+0.55 (+0.31, +0.80)** | **+0.62 (+0.31, +0.94)** |
| | Change in pain while walking on flat surface | |
| Whole group | **+0.56 (+0.35, +0.77)** | **+0.49 (+0.20, +0.78)** |
| | Change in pain while climbing stairs | |
| Whole group | **+0.33 (+0.02, +0.65)** | **+0.59 (+0.15, +1.02)** |
| | Change in pain in non-weight bearing | |
| Whole group | **+1.34 (+0.90, +1.78)** | **+1.18 (+0.56, +1.80)** |
| | Change in pain in weight bearing | |
| Whole group | **+1.49 (+0.82, +2.16)** | **+1.66 (+0.75, +2.58)** |

a= Adjusted for age, sex, BMI, offspring-control status, change in BMLs, change in cartilage defects, change in meniscal extrusion, change in effusion, history of knee injury and ROA at visit-1.
Bold font denotes statistically significant (p=<0.05) results
**(Note: Significant offspring-control interaction at all sites and sub-scales for the association between change in meniscal tears and change in pain)**

### 7.3.4 Structural changes

Table 7.4 describes the association between change in meniscal tears and knee structures on MRI over 8 years. Change in meniscal tears was independently associated with cartilage volume loss in the medial compartment only, increases in medial, lateral and total tibiofemoral BML area and with a higher risk of change in medial meniscal extrusion.

There was no significant association between change in meniscal tears and change in cartilage defects at any site in the fully adjusted model.

Only two participants underwent knee surgery between baseline and visit-3 and on both occasions the surgery was not a menisectomy or a joint replacement. Further adjustment for knee surgery did not change the effect size considerably for any of the associations described earlier (data not shown).

**Table 7.4.** Association between change in meniscal tears and knee structures on MRI over 8 years

| | β (95%CI) Adjusted[a] | β (95%CI) Adjusted[a] | Risk ratio(95%CI) Adjusted[a] |
|---|---|---|---|
| Change in tears (site) | Cartilage volume loss | Change in BMLs | Change in meniscal extrusion |
| | Total tibiofemoral | Total tibiofemoral | Total knee |
| Total knee | -52 (-208, +102) | **+0.41 (+0.29, +0.52)** | N/A |
| | Medial tibiofemoral | Medial tibiofemoral | Medial meniscus |
| Total medial | **-176 (-302, -49)** | **+0.33 (+0.22, +0.43)** | **1.53 (1.14, 2.03)** |
| | Lateral tibiofemoral | Lateral tibiofemoral | Lateral meniscus |
| Total lateral | +143 (-731, +1018) | **+0.26 (+0.10, +0.41)** | N/A |

a= adjusted for age, sex, bmi, offspring-control status, cartilage volume loss, change in BMLs, cartilage defects and meniscal extrusion, and ROA at visit-1
Bold font denotes statistically significant (p=<0.05) results
**(No significant offspring-control interaction at any site for the association between change in meniscal tears and change in BMLs)**
Note: Not enough change in lateral meniscal extrusion for analysis due to lack of power

## 7.4 Discussion

This study documents the natural history of meniscal tears over 8 years. In this midlife cohort meniscal tears were common with 22% of the participants suffering from at least one. 16% of the participants showed an increase in severity and none improved over 8 years. BMI and osteophytes independently predicted an increase in meniscal tears over 8 years. Change in meniscal tears was independently associated with an increase in knee pain severity, with offspring showing a greater increase in the severity of pain per unit change in meniscal tears compared to the control group. Change in meniscal tears was independently associated with cartilage volume loss, change in BMLs and meniscal extrusion over 8 years.

Majority of the meniscal tears (55/63) at visit-2 affected the medial meniscus. Medial posterior site showed the highest prevalence followed my medial body sites. Previous studies by Englund *et al.* [192] in older adults and by K. A Beattie *et al.* [197] in middle-aged adults showed a similar distribution in cross-sectional studies as well. Although the majority of the menisci remained stable over the course of 8 years, 16% showed an increase in severity over time. Again medial posterior was the most commonly affected site for both incident meniscal tears and worsening meniscal tear grades. Of note, none of the meniscal tears improved over the course of the study, unlike other knee structures such as BMLs [198] and cartilage defects [89] as previously shown in this cohort. Previously Dillon *et al.* [199] followed 22 patients with 27 intra-meniscal lesions with signal intensity changes on MRI but no tears on arthroscopy. After 27 months only 2 completely disappeared. Similarly Boegard *et al.* [200], followed 47 patients and found that only 2 meniscal tears out of 54 improved and none disappeared over 2 years. Meniscal tears, unlike other knee structures, do not seem to have the capacity to regenerate or improve over time. Slight discrepancies in the above mentioned studies could be due different populations, a longer follow-up period resulting in less measurement error in the present study and a possibly a more severe disease process in the offspring sub-group.

High BMI was the most consistent independent risk factor for increase in meniscal tear severity. A previous cross-sectional study from the present cohort showed that a higher BMI is positively associated with prevalent meniscal tears [94]. Our findings are consistent with Baker *et al.* [201] but differ from Englund *et al.* [142], who found a significant association

between BMI and meniscal extrusion but not tears. A recent meta-analysis examining risk factors for meniscal tears concluded that a high BMI is a moderate risk factor for developing meniscal tears along with occupational and recreational joint loading [202]. Osteophytes at visit-1 also predicted worsening of meniscal tears. Osteophytes are thought to be an early instigating factor in the OA causal pathway and their true prevalence is under estimated on radiographs [203]. Beattie *et al.* [197] showed, using peripheral MRI, that many peripheral osteophytes are missed by standard radiographs and their presence corresponds with degenerative meniscal changes at the same site. Presence of osteophytes in our study also showed a significant association with change in meniscal tears at the peripheries (anterior and posterior) and not at the meniscal body site. Interestingly, history of knee injury was not independently associated with meniscal tear increase. Previously, Englund *et al.* [142] have shown that history of knee injury is a strong risk factor for developing meniscal tears but they did not adjust for potential confounders. Similarly, we found a significant association between knee injury and meniscal tears in unadjusted analysis but this association did not persist in the fully adjusted model. These findings suggest that the changes in meniscal tears are not due to mechanical factors only and are mainly a part of an active osteoarthritic process.

Previously in this cohort, we showed a cross-sectional association between presence of meniscal tears and increased pain [94]. In a longitudinal study, Zanetti *et al.* [195] found that asymptomatic participants with a meniscal tear are more likely to develop knee pain than participants without one. Englund *et al.* [75] on the other hand concluded that any association between meniscal damage and knee pain seems to be present because both pain and meniscal damage are related to OA and not because of a direct link between the two. Our study is the first study to show an independent longitudinal association between increasing severity of meniscal tears and worsening pain, including pain on all individual WOMAC sub-scales, as well as both weight bearing and non-weight bearing pain. Previous studies have also suggested that meniscal tears appear to cause symptoms only when macerated tears extrude and damage collateral ligaments or when bone marrow abnormalities are present [204]. Results in this study were independent of change in meniscal extrusion and BMLs as well as localised inflammation as assessed by knee effusion, suggesting meniscal tears may be one of the most important knee structures in relation to pain.

Every unit increase in meniscal tears in the offspring group resulted in a greater increase in pain compared to the controls. Previously in this cohort, we found similar differences between the two groups when looking at the association between change in BMLs and pain [198]. A possible explanation could be the differences in the pain perception pathways of the two groups. Of note, polymorphisms in COMT and TRPV1 genes have recently been identified which could alter the processing of nociceptive pain associated with OA [43]. Another possible explanation could be that meniscal pathology in the offspring is morphologically different but this could not be differentiated on MRI.

Biomechanical studies have shown that the function of the meniscus is to reduce contact stress by enlarging the contact surface and shock absorption [205]. Meniscal function can be either lost due to meniscal tears or meniscal extrusion. Meniscal tears, especially macerated tears, are a possible risk factor for meniscal extrusion [206] and findings from this study confirm this. Loss of meniscal function can potentially damage articular cartilage and sub-chondral bone. Cross-sectional studies have shown that prevalent meniscal tears are associated with decreased cartilage volume [94] and BMLs [207]. Chang *et al.* [208] showed that meniscal tears are longitudinally associated with site specific cartilage loss. Findings in this study are in agreement with the latter study, as we found that meniscal tear increases were associated with medial cartilage loss independent of other knee structural changes. The present study is also the first to show a longitudinal association between increase in meniscal damage and increase in BML size. Menisci aid in load distribution and BMLs have been shown to be a consequence of abnormal loading within the knee joint [209], which explains the association between the increasing severity of these structural abnormalities. High BMI and osteophytes are possibly the early instigating factors that predict increasing severity of meniscal tears and then change in meniscal tears is associated with other structural changes such as meniscal extrusion, cartilage volume loss and BMLs.

A strength of our study is that it has the longest follow-up period of any OA cohort using MRI. A limitation of our study is a significant loss to follow up. Loss to follow-up can be a potential source of bias, however re-analysis of the data using inverse probability weighting did not change any of the results, indicating robust results. This cohort also has a wide age range (28-63 years old) as the inclusion criteria did not specify any specific age range. However, all the results described in this study were adjusted for age. Another limitation was

the absence of radiographs at visit-2 of the study, as we did not anticipate any major changes on radiographs due to young mean-age of the cohort with a low osteoarthritis disease burden and a short follow-up period of 2 years. Our study demonstrated an independent association between change in meniscal tears and worsening knee pain. However, the changes in the knee OA are remarkably collinear. Although we did adjust for other co-pathologies accounting for knee pain, an ideal design would be a long-term study with global knee structural assessment at multiple time points and a case-cross over design. Furthermore, we did not analyse different types of simple tears (longitudinal, oblique, radial or horizontal) separately due to a low number of individual lesions and hence insufficient power for analysis.

## Conclusion

Change in meniscal tears shares common risk factors with knee OA and is independently associated with worsening knee pain and structural damage suggesting that meniscal tears are on the knee OA causal pathway.

# CHAPTER EIGHT

## Natural History and Clinical Significance of Cartilage Defects over 10 Years

# 8.1 Introduction

Knee cartilage defects are a common finding in young healthy adults and in people with early osteoarthritis (OA) [89, 210] when the prevalence of other co-pathology is lower [211]. Initially they were thought to result from knee trauma only but recent evidence suggests otherwise [196]. Studies using MRI to study OA have suggested that cartilage defects can result as part of an active OA process [210, 212]. Cartilage degeneration in the form of defects is an early instigating factor in OA cascade and is thought to precede cartilage volume loss [113, 141] and is associated with radiographic osteoarthritis (ROA) [113, 212].

Our understanding of the pathophysiology of cartilage defects is however incomplete. Short term data from the present cohort over 2 years [89] showed that prevalent cartilage defects and change in defects predicted site specific cartilage volume loss. Another study, using a similar methodology, found a similar association at the patellar site only [213]. Secondly, the association between cartilage defects and pain or function is controversial as cartilage is an aneural structure. A study by Baum *et al.* [90] suggested that only prevalent focal cartilage lesions are significantly associated with knee pain and found no such associations with meniscal pathologies, bone marrow lesions (BMLs), effusion and ligamentous lesions. A recent systematic review [96] looking at the association between knee abnormalities and knee pain found no significant association between cartilage defects and pain. Lastly, studies have mostly focused on the medial tibiofemoral compartment. However, the prevalence of cartilage defects is relatively higher in the lateral compartment compared to the other abnormalities such as meniscal pathology [212] and BMLs [214, 215], and might play a more crucial role in lateral compartment OA progression.

Studies looking at the natural history of cartilage defects thus far have been short-term with no more than two study time points and did not account for global knee structural pathologies. So the aim of this study was to describe the natural history, predictors and structural/ symptomatic correlates of cartilage defects in a midlife cohort over 10 years.

# 8.2 Methods

## 8.2.1 Study subjects

This study was conducted as part of the Offspring study [102], a population-based study that began in Southern Tasmania in June 2000. Matched sampling was used to recruit the study participants. Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000 [152]. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiographs when possible. The other half were age and sex matched controls, randomly selected from the population with no history of knee OA in either parent. This study includes data from the baseline visit, 2 year and 10-year follow-up visits.

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants. Participants were excluded if they had a contraindication to MRI, underwent knee replacement surgery or did or after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

## 8.2.2 Anthropometrics

Weight was measured to the nearest 0.1 kg (Seca Delta Model 707). Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated ($kg/m^2$).

- Knee joint injury and surgery
- History of knee joint injury was assessed at all three visits using a self-administered questionnaire [196] which included the following questions:
- “Have you ever had a previous knee injury which resulted in non-weight bearing treatment for 24 hours or more?”
- “If yes, then which knee?”
- “Please provide further details about the injury”
- Only right knee injuries were included in the analysis as MRI scans were on the right knee.

### 8.2.3 Knee pain

Knee pain was assessed by self-administered questionnaire using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [93] at visit-2 and 3. Five categories of pain (walking on flat surface, going up or down stairs, at night, sitting or lying, and standing upright) were assessed separately with a 10-point scale from 0 (no pain) to 10 (most severe pain). Each category was summed to create a total pain score (range 0 to 50). Furthermore, the five categories were clinically categorized into weight-bearing pain (including walking on flat surface, going up or down stairs and standing) and non-weight-bearing pain (including pain at night and sitting or lying).

### 8.2.4 Magnetic resonance imaging

MRI of the right knee was performed as described previously [104, 198, 216]. Knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Picker International, USA) using a commercial transmit-receive extremity coil. The following image sequence was used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 ms, echo time 12 ms, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an inter-slice-gap (at all three visits); and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256×256 matrix, slice thickness of 4 mm with an inter-slice gap of 0.5–1.0 mm (at visit 2 and 3 only).

### 8.2.5 Cartilage defects

Cartilage defects were assessed on T1-weighted gradient echo MR images at the baseline, visit-2 and visit-3. Cartilage defects were graded at the medial tibial, medial femoral, lateral tibial, lateral femoral and patellar sites on a 0-4 scale (grade-0=normal cartilage; grade-1=focal blistering and intra-cartilaginous low-signal intensity area with an intact surface and bottom; grade-2=irregularities on the surface or bottom and loss of thickness of less than 50%; grade-3=deep ulceration with loss of thickness of more than 50%; grade-4=full-

thickness chondral wear with exposure of sub-chondral bone), as previously described. A cartilage defect also had to be present in at least two consecutive slices. If multiple defects existed at one site, the highest grade was used. Intra-observer reliability (expressed as intra-class correlation coefficient (ICC)) ranged from 0.89-0.90. Inter-observer reliability was assessed in 50 MR images and yielded an ICC of 0.85-0.90.

### 8.2.6 Cartilage volume

Tibial and patellar cartilage volumes were assessed on T1-weighted gradient echo MR images using Osiris (University of Geneva, Switzerland) software as previously described [104, 109]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Canada), as previously described [110, 111].

Absolute cartilage volume loss was calculated as: follow-up total cartilage volume - baseline total cartilage volume.

### 8.2.7 Meniscal tears

Meniscal tears were assessed on T2-weighted fat saturated MR images at visit-2 and 3 of the study as previously described [110]. The proportion of the menisci affected by a tear was scored separately (0-2 scale; 0=absence of a tear, 1=simple tears of different types (longitudinal, oblique, radial or horizontal) signifying loss<50% area of meniscal tissue, 2=complex tear signifying loss>50% area of meniscal tissue) at the anterior, middle, and posterior horns. Anterior, middle and posterior scores were summed to create medial and lateral meniscal tear scores.

### 8.2.8 Meniscal extrusion

The extent of meniscal extrusion on the medial or lateral edges of the tibial femoral joint space, not including the osteophytes, was evaluated at baseline, visit-2 and visit-3 for the anterior, body, and posterior horns of the menisci, as previously described [111]. A score

from 0 to 2 was used (0=no extrusion, 1=partial meniscal extrusion, and 2=complete meniscal extrusion with no contact with the joint space). The scores of anterior, body and posterior horns of medial or lateral menisci were summed to create a total meniscal extrusion score for each of the medial and lateral tibio-femoral compartment [110].

### 8.2.9 Bone marrow lesions

BMLs were assessed on T2-weighted fat saturated MR images at visit-2 and 3 at medial tibial, lateral tibial, medial femoral, lateral femoral and patellar sites. BMLs were defined as areas of increased signal adjacent to the subcortical bone and were measured as the maximum area of the lesion in a specific compartment, as described previously [198].

### 8.2.10 Effusion

Effusion was assessed in the supra-patellar pouch on T2-weighted fat saturated MR images at visit-2 and 3 on a 0-3 scale as previously described [217]. Pathological effusion was defined as any effusion score ≥2.

### 8.2.11 Radiography

A standing antero-posterior semi-flexed view of the right knee (at 15° flexion) was performed in all participants at baseline and visit-3. Radiographs were scored individually for osteophytes and JSN on a scale of 0–3 [84], according to the OARSI guidelines [82]. Radiographs were read as paired by two readers simultaneously. The presence of ROA was defined as any score ≥1 for JSN or osteophytes.

For all the structures described above, medial and lateral tibio-femoral scores were added together to generate total tibio-femoral scores. Similarly, total tibio-femoral and patellar scores were added to generate total knee scores.

Readers for all the scans were either musculoskeletal radiologists with several years of experience in OA research or health professionals trained by musculoskeletal radiologists. Readers were not blinded to the chronological sequence of the radiographs and MRI scans.

### 8.2.12 Statistical analysis

Change in all MRI and radiographic structures were calculated as: Visit-3 score – Baseline/Visit-2 score.

Change in total knee cartilage defects was dichotomised as any increase or no increase (decrease in severity or a stable score) in the severity of the mean cartilage defects score over ten years to describe the baseline characteristics of the study participants.

T-tests and Chi-square tests were used to describe the baseline characteristics of the participants with or without any increase in mean cartilage defects score.

Descriptive analyses were used to describe the site-specific natural history of cartilage defects over 10 years. T-tests were used to describe the differences between the offspring and control groups for site-specific change in mean cartilage defects and the difference in the number of incident or new cartilage defects at each site.

Box-plots were used to describe the association between compartment specific severity of cartilage defects at baseline and cartilage volume loss over 10 years.

Linear regression analysis was used to examine the predictors of change in cartilage defects and to describe the association between change in cartilage defects and change in WOMAC pain scale and other structural pathologies assessed on MRI. Linear regression using mixed methods analysis was used to examine the association between change in cartilage defects and cartilage volume loss as both were assessed at all three time points.

A P-value of less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 12.0 for windows (StataCorp LP).

## 8.3 Results

Of the 372 participants included in the Offspring study, 220 between the ages of 26 and 61 years were followed-up for 10 years. 5 participants were excluded from the present study due to missing data. There were no significant differences in the baseline characteristics between those lost to follow-up (n=152) and the participants in our study in terms of age, sex, BMI, baseline prevalence of cartilage defects and radiographic OA (data not shown).

Figure 8.1A describes the site-specific prevalence of cartilage defects at baseline. 44% of the participants had at least one cartilage defect at any site at baseline. The patellar site (25.1%) had the highest prevalence followed by medial tibial (14.4%), medial femoral (13%), lateral tibial (10.4%) and lateral femoral (8.7%) sites. Figure 8.1B describes the site-specific change in cartilage defects over 10 years. Most of these defects remained stable over 10 years. 26% increased in severity with medial tibial (30%) being the most commonly effected site. 13% of the cartilage defects present at baseline decreased in severity over 10 years with patellar site having the highest percentage (17%) of defects that decreased in severity.

Offspring showed a higher increase in the severity of the cartilage defects compared to the controls, however these differences were statistically significant only at the medial tibial and the medial femoral sites (data not shown). There was a similar trend for incident (new cartilage defects not present at baseline) cartilage defects but the difference was statistically significant only at the medial femoral site (data not shown).

Table 8.1 describes the baseline characteristics of participants with and without any increase in mean cartilage defects score over 10 years. Participants with any increase in cartilage defects severity had a significantly higher prevalence of JSN and BMLs compared to participants with no increase.

Figure 8.2 describes the association between compartment specific cartilage defects at baseline and absolute cartilage volume loss over 10 years. Per unit increase in severity of lateral tibio-femoral but not medial cartilage defects predicted cartilage volume loss over 10 years.

Table 8.2 describes the predictors of change in cartilage defects. Both the presence and severity (per grade) of JSN and osteophytes and severity (per grade) of supra-patellar

effusion predicted change in tibio-femoral and total knee cartilage defects in unadjusted analyses but these associations only persisted for JSN in the fully adjusted model. Only the severity (per unit area) of BMLs independently predicted change in tibio-femoral cartilage defects. There were no significant associations between meniscal pathologies and change in cartilage defects.

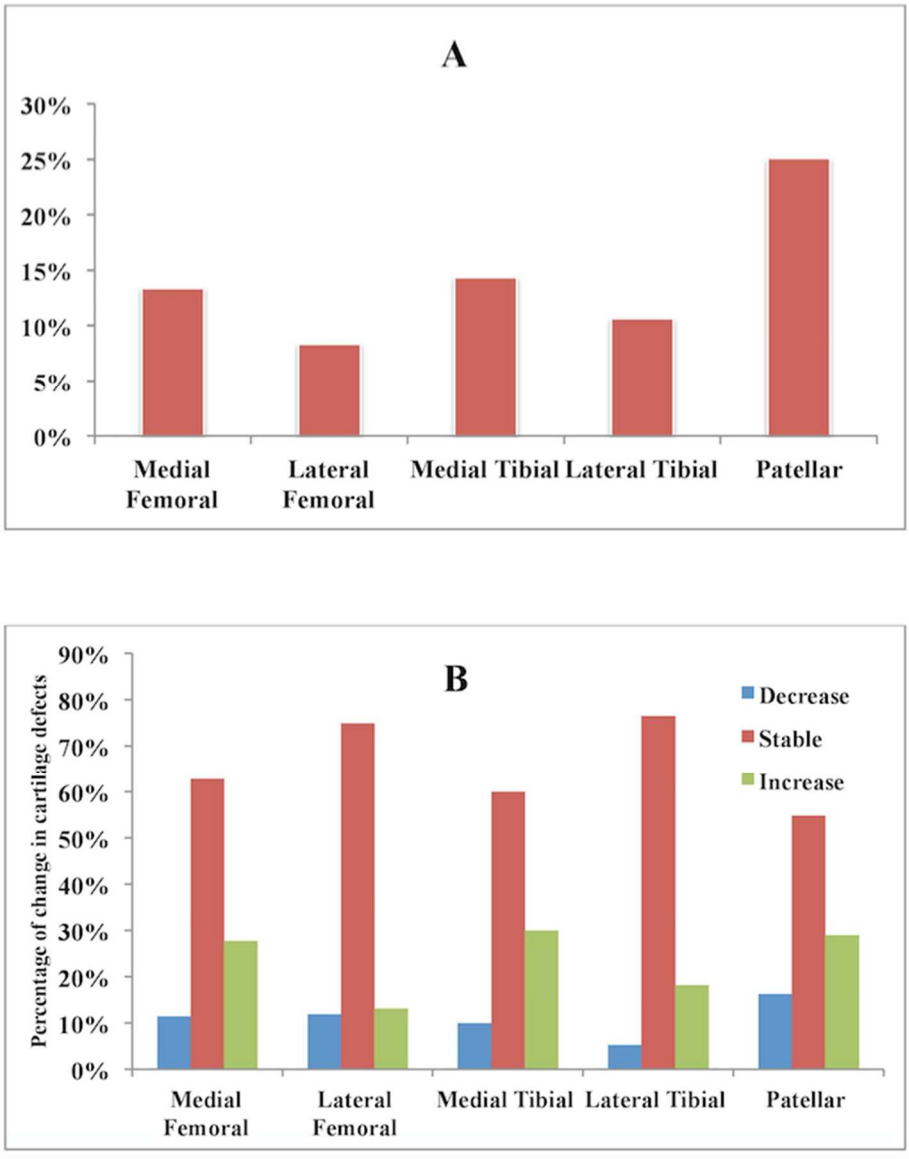


**Figure 8.1**. Natural history of cartilage defects. A) Site specific prevalence of cartilage defects at baseline. B) Site-specific change in cartilage defects over 10 years

**Table 8.1.** Characteristics of participants with and without any increase in mean cartilage defects score over 10 years

| | Any increase (n=146) | No increase (n=69) | p-value |
|---|---|---|---|
| Age (years) | 45.1 ± 6.7 | 45.5 ± 6.9 | 0.691 |
| Male (%)* | 42 % | 41 % | 0.794 |
| BMI (kg/m$^2$) | 27.1 ± 4.9 | 27.5 ± 5.1 | 0.599 |
| Offspring (%)* | 56 % | 45 % | 0.123 |
| Ever smoked (%)* | 42 % | 46 % | 0.525 |
| Knee Injury (%)* | 19 % | 17 % | 0.753 |
| Any JSN (%)* | **20 %** | **10 %** | **0.045** |
| Any osteophytes (%)* | 13 % | 9 % | 0.357 |
| WOMAC (mean) | 2.8 ± 4.9 | 2.9 ± 5.7 | 0.818 |
| Total knee cartilage volume (mm$^3$) | 17739.1 ± 4330.8 | 16824.3 ± 3563.4 | 0.151 |
| Any meniscal tear (%)* | 23 % | 15 % | 0.218 |
| Any meniscal extrusion (%)* | 9 % | 6 % | 0.431 |
| Any effusion (%)* | 42 % | 29 % | 0.079 |
| Any bone marrow lesion (%)* | **70 %** | **53 %** | **0.021** |

Mean ± standard deviation except for percentages; *Determined by Chi square test, others by t-test

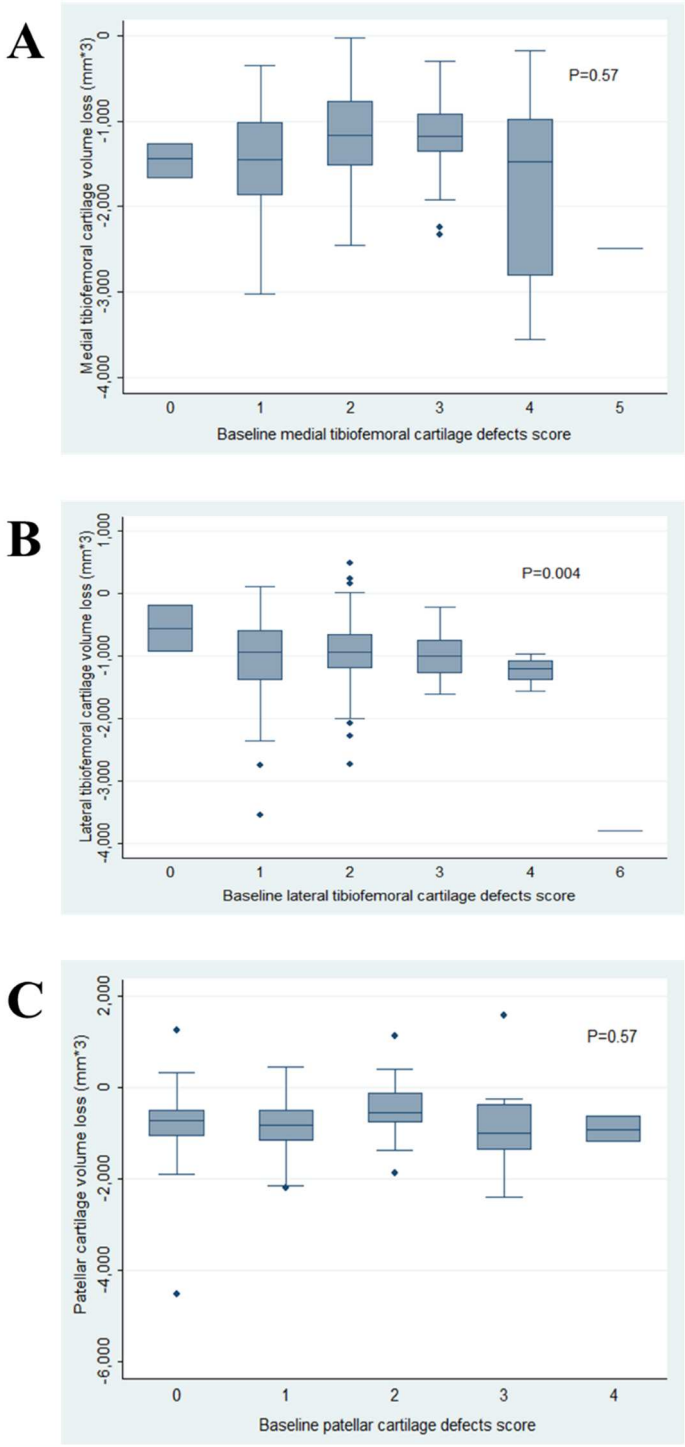


**Figure 8.2.** Association between cartilage defects at baseline and cartilage volume loss over 10 years. A) Medial tibio-femoral compartment. B) Lateral tibio-femoral compartment. C) Patellar compartment

**Table 8.2** Predictors of change in cartilage defects

| | Unadjusted β (95%CI) | Adjusted[a] β (95%CI) | Unadjusted β (95%CI) | Adjusted[a] β (95%CI) |
|---|---|---|---|---|
| | | **Change in cartilage defects** | | |
| | **Total tibiofemoral** | | **Total knee** | |
| Age | -0.09 (-0.58, +0.41) | -0.38 (-0.94, +0.17) | +0.01 (-0.56, +0.58) | -0.39 (-1.02, +0.25) |
| Sex (Female) | -0.26 (-0.76, +0.23) | -0.03 (-0.82, +0.76) | -0.27 (-0.85, +0.31) | -0.24 (-0.85, +0.96) |
| BMI | +0.02 (-0.03, +0.07) | +0.01 (-0.04, +0.06) | +0.02 (-0.03, +0.08) | +0.01 (-0.05, +0.07) |
| Knee Injury | +0.14 (-0.49, +0.77) | -0.25 (-0.95, +0.45) | +0.41 (-0.32, +1.14) | -0.07 (-0.87, +0.74) |
| Any JSN | **+0.95 (+0.16, +1.31)** | **+0.83 (+0.32, +1.60)** | **+1.05 (+0.31, +1.80)** | **+1.13 (+0.10, +2.18)** |
| Severity of JSN | **+0.79 (+0.21, +1.38)** | **+0.86 (+0.02, +1.70)** | **+0.89 (+0.19, +1.58)** | **+1.04 (+0.10, +1.99)** |
| Any osteophytes | **+0.79 (+0.04, +1.53)** | +0.47 (-0.74, +1.69) | **+0.91 (+0.03, +1.79)** | +0.42 (-0.96, +1.81) |
| Severity of osteophytes | **+0.56 (+0.21, +0.91)** | +0.12 (-0.51, +0.75) | **+0.62 (+0.21, +1.03)** | +0.03 (-0.69, +0.74) |
| Any meniscal extrusion | +1.40 (+0.50, +2.30) | +0.72 (-0.40, +1.83) | +1.54 (+0.50, +2.58) | +0.87 (-0.40, +2.14) |
| Severity of meniscal extrusion | +0.66 (+0.18, +1.15) | +0.12 (-0.49, +0.74) | +0.79 (+0.22, +1.36) | +0.22 (-0.48, +0.91) |
| Any meniscal tear* | +0.21 (-0.36, +0.78) | +0.18 (-0.47, +0.83) | +0.32 (-0.30, +0.95) | +0.34 (-0.37, +1.04) |
| Severity of meniscal tears* | +0.19 (-0.02, +0.41) | +0.03 (-0.27, +0.34) | +0.22 (-0.02, +0.46) | +0.05 (-0.29, +0.38) |
| Any BMLs* | +0.42 (-0.05, +0.89) | +0.49 (-0.01, +0.99) | +0.59 (+0.05, +1.14) | +0.38 (-0.20, +0.96) |
| Severity of BMLs* | **+0.67 (+0.13, +0.78)** | **+0.64 (+0.10, +1.20)** | +0.33 (-0.07, +0.72) | +0.36 (-0.09, +0.85) |
| Any effusion* | +0.16 (-0.31, +0.62) | -0.18 (-0.70, +0.34) | +0.14 (-0.38, +0.66) | -0.34 (-0.91, +0.22) |
| Severity of effusion* | **+0.25 (+0.06, +0.43)** | +0.02 (-0.17, +0.21) | **+0.40 (+0.15, +0.64)** | +0.10 (-0.16, +0.35) |

aAdjusted for age, sex, bmi, offspring-control status, meniscal tears, meniscal extrusion, cartilage volume, bone marrow lesions, pathological effusion and radiographic osteoarthritis
*Predicted change in cartilage defects over 8 years (between visits 2 and 3)

Table 8.3 describes the association between change in cartilage defects and structural changes assessed on MRI. Change in cartilage defects was independently associated with absolute cartilage volume loss (using mixed method analysis) at the lateral tibio-femoral, total tibio-femoral and total knee sites. There was an independent association between change in BMLs and change in cartilage defects in the lateral tibio-femoral compartment only. There were no significant associations between change in cartilage defects and change in meniscal pathologies or effusion.

Table 8.4 describes the association between change in cartilage defects and change in WOMAC (pain) over 8 years. Change in cartilage defects was significantly associated with change in pain at the lateral and total tibio-femoral compartments in the unadjusted analysis but these associations did not persist in the fully adjusted model.

**Table 8.3.** Association between change in cartilage defects and structural changes assessed on MRI

| | Cartilage volume loss | Change in meniscal extrusion | Change in meniscal tears | Change in bone marrow lesions | Change in pathological effusion |
|---|---|---|---|---|---|
| Change in cartilage defects (site) | Adjusted β (95%CI) | Adjusted β (95%CI) | Adjusted β (95%CI) | Adjusted β (95%CI) | Adjusted β (95%CI) |
| Medial tibiofemoral | -33.70 (-88.49, +21.09) | -0.01 (-0.40, +0.38) | -0.09 (-0.41, +0.23) | -0.02 (-0.08, +0.04) | +0.23 (-0.10, +0.57) |
| Lateral tibiofemoral | **-77.67 (-137.51, -17.84)** | Not enough change | -0.21 (-0.50, +0.09) | **+0.07 (+0.01, +0.13)** | -0.05 (-0.26, +0.17) |
| Patellar | -34.64 (-90.90, +21.59) | -0.06 (-0.26, +0.15) | +0.16 (-0.03, +0.29) | -0.01 (-0.09, +0.06) | -0.09 (-0.27, +0.10) |
| Total tibiofemoral | **-152.52 (-210.60, -94.44)** | +0.13 (-0.30, +0.56) | -0.22 (-0.52, +0.08) | +0.06 (-0.01, +0.13) | +0.24 (-0.15, +0.62) |
| Total knee | **-123.87 (-193.24, -54.50)** | +0.08 (-0.39, +0.55) | -0.02 (-0.35, +0.31) | +0.05 (-0.02, +0.12) | +0.15 (-0.28, +0.58) |

aAdjusted for age, sex, bmi, offspring-control status, cartilage volume loss, change in meniscal tears, change in meniscal extrusion, change in BMLs, change in supra-patellar effusion and radiographic osteoarthritis at baseline

**Table 8.4**. Association between change in cartilage defects and change in pain

| | Unadjusted β (95%CI) | Adjusted β (95%CI) |
|---|---|---|
| Change in cartilage defects (site) | Change in WOMAC (pain) over 8 years | |
| Medial tibiofemoral | +0.36 (-0.31, +1.05) | +0.48 (-0.35, +1.32) |
| Lateral tibiofemoral | **+1.21 (+0.17, +2.25)** | +1.17 (-0.18, +2.52) |
| Patellar | -0.34 (-1.65, +0.86) | -0.95 (-2.70, +0.75) |
| Total tibiofemoral | **+0.61 (+0.05, +1.18)** | +0.55 (-0.20, +1.30) |
| Total knee | +0.43 (-0.08, +0.94) | +0.24 (-0.45, +0.93) |

aAdjusted for age, sex, bmi, offspring-control status, change in bone marrow lesion, change in meniscal tears, change in meniscal extrusion, change in supra-patellar effusion and radiographic osteoarthritis at baseline

## 8.4 Discussion

This study documents the natural history of cartilage defects over 10 years with data available at 3 time points. In this midlife cohort cartilage defects were common with 44% of the participants suffering from at least one at the baseline visit. Most of these defects remained stable, whereas 26% increased and 13% decreased in severity over 10 years. Severity of cartilage defects at baseline predicted cartilage volume loss only in the lateral tibio-femoral compartment. Presence and severity JSN and severity of BMLs and family history of knee OA predicted an increase in cartilage defects over 10 years. Change in cartilage defects in turn was associated with changes in BMLs and cartilage volume loss. There was no independent association between change in cartilage defects and increase in pain severity over 10 years.

A minority of the cartilage defects present at baseline increased in severity over 10 years in this cohort. In previous longitudinal MRI studies, progression rates of cartilage defects based on semi-quantitative scoring have been reported to vary from 17% to 68% [89, 200, 210, 218-220]. This wide range of progression rates is due to a number of factors. Amin *et al.* [218] reported progression of cartilage damage in 46% and 22% of knees in the medial and lateral compartments, respectively, over 2.5 years in symptomatic subjects. Similarly, Davies-Tuck *et al.* [219] reported worsening of cartilage defects of 32-68% at different joint sites over 2 years. However, both of these cohorts had a higher prevalence of ROA compared to the Offspring study. The former cohort consisted of participants of whom 72% had a (Kellgren and Lawrence) KL grade $\geq 2$ whereas the latter was a convenience sample of subjects with ROA. Several studies [218-220] have shown the progression of cartilage defects increases with more severe radiographic disease, which explains a lower rate of progression in this study despite a considerably longer follow-up period. In another study Cibere *et al*. [210] showed progression rate of 22.7% over 3 years despite the fact that their cohort was a bit older and had a slightly higher prevalence of ROA compared to the Offspring study. However, they used a more conservative definition of cartilage defects progression that can explain a slightly lower progression rate in their study.

Regression of cartilage defects is a controversial topic. In this cohort of young healthy middle-aged adults 13% of the cartilage defects decreased in severity over 10 years.

Experimental studies in animals have shown that cartilage has significant capacity to self-repair especially for small sized hyaline or fibrocartilage defects [221, 222]. We have previously shown that regression of cartilage defects is rare in older adults [141], using the same assessment protocol, indicating that fibrocartilage loses the ability to self-repair as we age. This could reflect declining mitotic and synthetic activity in chondrocytes that occurs with age in cartilage [223], with fewer cartilage defects regressing over time due to less self-repair in older adults. Similarly, some recent studies in middle-aged cohorts, using different assessment protocols, have shown that cartilage defects can regress over time [219, 224].

Cartilage defects are traditionally thought to precede cartilage volume loss, however not many studies have actually shown this relationship. Cross-sectional studies have shown that prevalent cartilage defects are negatively associated with cartilage volume and positively associated with cartilage breakdown products [113]. Two-year data from the Offspring study [108] and another longitudinal study [225] conducted in 86 middle-aged men and women in Melbourne showed that baseline cartilage defects predict cartilage volume loss in the medial tibiofemoral compartment. Data from this study is somewhat consistent with these findings as cartilage defects independently predicted cartilage volume loss in the lateral compartment. Earlier studies did not account for both the BMLs and meniscal tears when looking at the association between cartilage defects and cartilage volume loss. 8-year longitudinal data from the Offspring study has shown that BMLs [198] and meniscal tears [226] are more common in the medial compartment and are associated with cartilage volume loss. After adjustment for these structural co-pathologies, we did not see any independent association between cartilage defects and cartilage volume loss in the medial compartment. Similarly, we have previously shown that baseline cartilage defects predict cartilage volume loss in a randomly selected sample of older adults from the community in all three compartments but the associations in the medial compartment did not persist after adjustment for BMLs [141]. However this study could not account for meniscal pathologies as all subjects had them. The longitudinal relationship between change in cartilage defects and other structural co-pathologies showed a similar trend. Change in cartilage defects was independently associated with cartilage volume loss, using mixed methods over three time-points, in the lateral compartment but not the medial and patellar compartments. Similarly change in cartilage defects was associated with change in BMLs in the lateral compartment only. Cartilage

defects are relatively more common in the lateral compartment compared to other co-pathologies and possibly play a more crucial role in the development of the overall disease process in the lateral compartment.

Several studies have shown a positive association between cartilage defects and knee pain, despite the fact that cartilage is an aneural structure. In a cross-sectional sub-sample of 126 middle-aged adults from Osteoarthritis Initiative (OAI) database, Baum *et al.* [90] found that elevated T-2 cartilage signals are associated with findings of pain in the early phase of OA, whereas among morphologic knee abnormalities only knee cartilage lesions are significantly associated with knee pain. Similarly, Javaid MK *et al*. [227] found that cartilage defects with a score >2 can significantly discriminate between painful and non-painful knees. However, in a recent systematic review Yusuf E *et al.* [96] found that the knee pain in OA is associated with BMLs and effusion/synovitis but not cartilage defects. Our data suggests the same as well. Change in cartilage defects was associated with increase in knee pain over 8 years in the univariable analysis but once we accounted for BMLs and effusion/synovitis there was no significant association between the two. Subchondral BMLs and effusion/synovitis that result from cartilage defects, or knee structural damage in general, explain most of the pain resulting from OA.

Our study has several strengths and weaknesses. The biggest strength of our study is the longest knee MRI data currently available with cartilage defects natural history data available at three time points. Secondly we accounted for global knee structural pathologies in our results. A weakness of our study was that, unlike cartilage defects, the data from T-2 weighted MR images and WOMAC pain scale data was available at only 2 time points. Secondly this data is from matched sample of middle-aged adults and is not representative of general population especially older adults with more established knee OA.

## Conclusion

Data from this midlife cohort suggests that cartilage defects are on the OA causal pathway for structure and symptoms especially in the lateral compartment. Unlike meniscal pathology, cartilage defects have the capacity to heal over time thus may be amenable to intervention.

# CHAPTER NINE

## Correlation Between Changes in Global Knee Structures Assessed on MRI and Radiographic Osteoarthritis Changes over Ten Years in a Mid-Life Cohort

# 9.1 Introduction

Knee osteoarthritis (OA) is one of the most common causes of disability in adults over the age of 60 [17]. Despite the increasing prevalence of OA worldwide, few effective treatments are available. A major impediment to the development of effective treatment options that would halt or delay the progression of the disease is the lack of a sensitive and reproducible outcome for clinical trials. Currently, clinical examination and measurement of joint space narrowing (JSN) and osteophytes on plain radiographs are the gold standard for diagnosing knee OA [79]. Increase in JSN (or change in joint space width (JSW)) is the only method approved by regulators to monitor progression in disease-modifying OA drug (DMOAD) and chondro-protective trials [80]. However, the reproducibility of this method is influenced by subject positioning and changes in the radio-anatomic alignment of the joint in serial examinations[31]. Furthermore, radiography is insensitive to early disease structural changes as an estimated 10% reduction in cartilage loss occurs before radiographic OA is detected [84]. It is also not very sensitive to change as it takes several years to detect progression of radiographic OA [84, 85].

JSN is traditionally considered a surrogate for cartilage volume and changes in joint space are attributed to cartilage loss. Extensive use of magnetic resonance imaging (MRI) over the last decade has shown that OA is a disease of the whole joint [212]. Structural changes, apart from cartilage volume loss, such as cartilage defects, meniscal tears and meniscal extrusion are also associated with JSN in cross-sectional studies [116] but there have been no long term studies examining change in these global knee measures and their independent contributions to changes in JSN (or osteophytes).

The aim of this study was to describe the correlation between change in structural abnormalities assessed on MRI and change in radiographs over 10 years in a midlife cohort.

## 9.2 Patients and Methods

### 9.2.1 Study Population

This study was conducted as part of the Offspring study, which is an ongoing population-based study [102]. The Offspring study began in southern Tasmania (primarily in the city of Hobart) in June 2000 (Figure 9.1). Matched sampling was used to recruit the study participants (mean age 45(26–61) years; 58% females). Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000 [228]. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiographs when possible. The other half were age and sex matched controls, randomly selected from the population with no history of knee OA in either parent. This study includes data from visit-1 (2000-01), visit-2 (2002-03) and visit-3 (2010-11) of the study.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants. Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). Participants were also excluded if they had undergone a knee replacement surgery or did so after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

### 9.2.2 Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$).

### 9.2.3 Knee joint injury and surgery

History of knee joint injury and surgery were assessed at all three visits using a self-administered questionnaire [196] which included the following questions :

- "Have you ever had a previous knee injury which resulted in non-weight bearing treatment for 24 hours or more?"
- "If yes, then which knee?"
- "Please provide further details about the injury"
- "Have you ever had a knee surgery?"
- "If yes, then which knee?"
- "Please provide further details about the surgery"

Only right knee injuries were included in the analysis as MRI scans were on the right knee.

### 9.2.4 Imaging

**MRI**

MRI of the right knee was performed as described previously [89, 104, 108]. Knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Picker International, USA) using a commercial transmit-receive extremity coil at the baseline visit, 2 year and 10 year follow up visits. The following image sequence was used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 msec, echo time 12 msec, field of view 16 cm, 60 partitions, 512×512–pixel matrix, slice thickness of 1.5 mm without an interslice-gap (at all three visits); and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256×256 matrix, slice thickness of 4 mm with an interslice gap of 0.5–1.0 mm (at visit 2 and 3 only).

The same scanner (same model and machine) was used at all the three visits for both T1-weighted fat-suppressed and T2-weighted fat saturation images.

**Cartilage volume**

Knee cartilage volume was evaluated at baseline and 10 years by one trained observer on T1-weighted gradient echo MR images. Knee cartilage volume was determined by means of image processing on an independent workstation at baseline and follow up. The volumes of individual cartilage plates (medial tibia and femora, and lateral tibia and femora) were isolated from the total volume by manually drawing dis-articulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 × 312 μm by 1.5 mm thickness, continuous sections) for the final three-dimensional rendering to calculate the cartilage volume.

Tibial cartilage volume was assessed using Osiris (University of Geneva, Switzerland) software as previously described [104, 109]. The coefficient of variation(CV) ranged from 2.1–2.2% for intra-observer repeatability [84]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Canada), as previously described [110-112]. The CV was approximately 2% for intra-observer and inter-scan repeatability [111]. Total cartilage volume was calculated as: tibial + femoral cartilage volume.

Independent readers assessed tibial and femoral cartilage volume at baseline and 10 years.

Change in cartilage volume was calculated as: follow-up total cartilage volume - baseline total cartilage volume.

**Cartilage defects**

Cartilage defects were assessed on T1-weighted gradient echo MR images by one trained observer at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites on a 0-4 scale, as previously described [108]: grade 0=normal cartilage; grade 1=focal blistering and intra-cartilaginous low-signal intensity area with an intact surface and base; grade 2=irregularities on the surface or base and loss of thickness <50%; grade 3=deep ulceration with loss of thickness >50%; and grade 4=full-thickness chondral wear with exposure of subchondral bone. The presence of any cartilage defect was defined as any score ≥2. Intraobserver reliability (expressed as intraclass correlation coefficient(ICC)) ranged from

0.89-0.90 [108]. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.85-0.90 [108].

**Meniscal tears**

Meniscal tears were assessed by one trained observer on T1-weighted gradient echo and T2-weighted (side by side) MR images at visit-2 and 3 of the study as previously described [110]. The proportion of the menisci affected by a tear was scored separately (0-2 scale; 0=absence of a tear, 1=simple tears of different types: longitudinal, oblique, radial or horizontal, 2=complex or macerated tears signifying loss>50% area of meniscal tissue) at the anterior, middle, and posterior horns. The presence of any meniscal tear was defined as any score ≥1. Anterior, middle and posterior scores were summed to create medial and lateral meniscal tear scores. The intra- and inter-observer correlation coefficient ranged from 0.86 to 0.96 [111]. Meniscal tears were measured at visits 2 and 3 of the Offspring study, 2 and 10 years after the baseline visit.

**Meniscal extrusion**

The extent of meniscal extrusion on the medial or lateral edges of the tibial femoral joint space, not including the osteophytes, was evaluated by one trained observer at baseline and at 10 years for the anterior, body, and posterior horns of the menisci, as previously described [111]. A score from 0 to 2 was used (0 = no extrusion, 1 = partial meniscal extrusion, and 2 = complete meniscal extrusion with no contact with the joint space). The presence of any meniscal extrusion was defined as any score ≥1. The scores of anterior, body and posterior horns of medial or lateral menisci were summed to create a total meniscal extrusion score for each of the medial and lateral tibiofemoral compartments which had a possible range from 0 to 6 [111].

### 9.2.5 Radiology

A standing anteroposterior semiflexed x-ray of the right knee was taken in all subjects at baseline and 10 years. The angle was kept to 10–15˚ by a purpose built goniometer. The tube to film and tube to tibial plateau angle was 90˚. Daily quality assurance was performed on the equipment. Radiographs were scored individually for osteophytes and JSN, as described previously [84]. Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial JSN, lateral JSN, medial osteophytes (femoral and tibial combined) and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International (OARSI) atlas [82]. A non-zero score in either JSN or osteophytosis was regarded as evidence of radiographic OA. Reproducibility was assessed in 50 radiographs, two weeks apart, and yielded an ICC of 0.99 for osteophytes and 0.98 for JSN [216].

Change in radiographic OA was calculated as: follow-up radiographic OA score - baseline radiographic OA score. Any increase in radiographic score over 10 years was defined as an increase ($\geq$1).

Readers for all the scans were either musculoskeletal radiologists with several years of experience in OA research or health professionals trained by musculoskeletal radiologists. All the scans were read by independent readers. All MRI structures were assessed independently as well with readers not aware of the severity of other structural abnormalities. Baseline and follow-up scans were read as paired. Readers were not blinded to the chronological sequence of the radiographs and MRI scans.

### 9.2.6 Statistical analysis

T-test and Chi square test were used to describe the characteristics of the study participants who had no change or any change in radiographic OA over 10 years.

Spearman ranked correlation analyses were used to examine the correlations between structural changes on MRI and radiographs. Absolute change in all MRI and radiographic

structures was calculated as: Visit-3 score – Baseline/Visit-2 score. Only absolute changes, regardless of magnitude and direction, were used to describe correlations between MRI and radiographic changes. Multivariable analyses were adjusted for age, sex, BMI, offspring-control status, change in cartilage volume, cartilage defects, meniscal tears and meniscal extrusion, and change in radiographic JSN/osteophytes.

Further analysis, using logistic regression, was performed to examine the association between no increase or any increase in the severity of MRI and radiographic structures. Dichotomised variables were used to describe no or any increase in the severity of MRI and radiographic structures (0-1 scale; 0=stable score or a decrease in score, 1=increase in score). Cartilage volume loss was dichotomised using mean cartilage volume loss over 10 years.

Interaction terms were calculated for all the above-mentioned correlations to see if the strength of correlation was significantly different between the offspring and controls. Only medial tibiofemoral compartment results are presented as the lateral compartment had limited change and the resultant analysis lacked sufficient power.

A p-value less than 0.05 (two-tailed) was considered statistically significant. All analyses were performed on Intercooled Stata V.12.0 for windows (StataCorp LP).

## 9.3 Results

Figure 9.1 is flow-chart describing the study population of the offspring study. A total of 219/372 participants (57% female, mean age 45) completed the study. 8 participants had missing radiographic or MRI data and were not included in the final analysis. There was no significant difference in baseline characteristics between those who completed the study and those lost to follow-up (follow-up vs loss to follow-up: age (years) 45.3 vs 45.1, p=0.80; sex (female%) 57 vs 59, p=0.74; BMI (kg/m$^2$) 27.2 vs 26.8, p=0.49; radiographic OA (%) 18 vs 15, p=0.48.

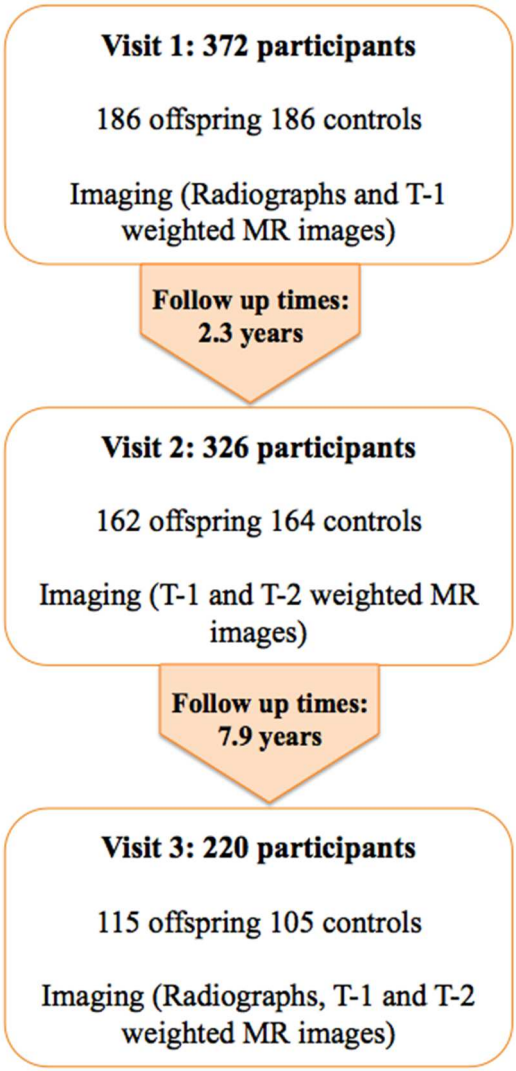


**Figure 9.1.** Flow chart of the Offspring study

32% (67/211) of the participants showed an increase in the medial radiographic OA severity with a mean increase in score of 0.49. All 211 participants, regardless of an increase or not in medial radiographic OA score, were included in the final correlation analysis. Mean absolute cartilage volume loss in the medial tibiofemoral compartment was -1284 $mm^3$ (19% lower than baseline).

Table 9.1 describes the characteristics of the study participants. First characteristics of the whole study population are presented and then the characteristics of the participants split by no or any change in medial radiographic OA over 10 years. Participants with any change had a significantly higher prevalence of radiographic OA and meniscal tears at baseline and a significantly higher percentage of participants who had any change in meniscal tears**.** There was no other significant difference in either demographic or structural characteristics between the two groups.

Table 9.2 describes the correlation between structural changes on MRI and radiographs. Change in meniscal tears showed the strongest correlation with change in both JSN and osteophytes in the fully adjusted model. Change in meniscal extrusion and cartilage defects also showed significant correlations with change in JSN but not with change in osteophytes. Cartilage loss showed weak and non-significant correlations with either change in JSN or osteophytes. There were no significant differences between the offspring and controls for any of the above mentioned correlations.

Further analysis was performed to describe the association between any increase, regardless of magnitude, in MRI and radiographic structures. Any increase in the severity of meniscal tears **(OR=+3.6 (95%CI +1.7, +7.6), p=0.001)** and extrusion **(OR=+2.3 (+1.1, +4.6), p=0.019)**, but not cartilage defects or volume, was significantly associated with any increase in JSN. Only increase in meniscal tears was associated with any increase in osteophytes **(OR=+2.8 (+1.3, +6.1), p=0.008)**.

Only two participants underwent knee surgery between baseline and visit-3 and on both occasions the surgery was not a meniscectomy or a joint replacement. Further adjustment for knee surgery and incident knee injury did not change the effect size considerably for any of the associations described earlier (data not shown).

**Table 9.1.** Characteristics of the study participants

| | **Whole population** | **No change in radiographic OA (n=144)** | **Any change in radiographic OA (n=67)** | **P-Value** |
|---|---|---|---|---|
| Age (years) | 45.2 | 45.4 | 44.9 | 0.635 |
| Female sex (%)* | 57 | 58 | 55 | 0.742 |
| BMI (kg/m$^2$) | 27.1 | 27.4 | 26.7 | 0.338 |
| Offspring (%)* | 51 | 50 | 54 | 0.614 |
| Any radiographic OA at baseline (%)* | 18 | **10** | **22** | **0.031** |
| Any medial meniscal tear at baseline (%)* | 20 | **16** | **30** | **0.031** |
| Any change in medial meniscal tears (%)* | 13 | **8** | **23** | **0.005** |
| Any medial meniscal extrusion at baseline (%)* | 8 | 8 | 6 | 0.529 |
| Any change in medial meniscal extrusion (%)* | 11 | 10 | 13 | 0.498 |
| Medial cartilage volume at baseline (mm$^3$)^ | 6766 | 6733 | 6887 | 0.558 |
| Medial cartilage volume loss (mm$^3$)^ | -1283 | -1276 | -1287 | 0.899 |
| Any medial cartilage defects at baseline (%)^* | 25 | 28 | 20 | 0.219 |
| Any change in medial cartilage defects (%)^* | 50 | 48 | 53 | 0.554 |

*Determined by Chi square test, all others by t-test, ^Sum of medial tibial and femoral

**Table 9.2.** Correlation between structural changes on MRI over 8-10 years and radiographic changes over 10 years

| | **Unadjusted** | | **Adjusted[a]** | | **Adjusted[b]** | |
|---|---|---|---|---|---|---|
| | **ρ** | **P-value** | **ρ** | **P-value** | **ρ** | **P-value** |
| | Change in medial meniscal tears over 8 years | | | | | |
| Change in medial JSN over 10 years | **+0.42** | **<0.01** | **+0.38** | **<0.01** | **+0.37** | **<0.01** |
| Change in medial osteophytes over 10 years | **+0.34** | **<0.01** | **+0.34** | **<0.01** | **+0.31** | **<0.01** |
| | Change in medial meniscal extrusion over 10 years | | | | | |
| Change in medial JSN over 10 years | **+0.30** | **<0.01** | **+0.27** | **<0.01** | **+0.22** | **<0.01** |
| Change in medial osteophytes over 10 years | **+0.14** | **0.03** | **+0.14** | **0.04** | +0.02 | 0.83 |
| | Medial cartilage volume loss over 10 years | | | | | |
| Change in medial JSN over 10 years | **-0.18** | **0.01** | -0.11 | 0.14 | -0.01 | 0.97 |
| Change in medial osteophytes over 10 years | -0.14 | 0.06 | **-0.17** | **0.02** | -0.12 | 0.14 |
| | Change in medial cartilage defects over 10 years | | | | | |
| Change in medial JSN over 10 years | +0.12 | 0.09 | +0.11 | 0.12 | **+0.16** | **0.04** |
| Change in medial osteophytes over 10 years | +0.02 | 0.74 | +0.01 | 0.94 | +0.02 | 0.79 |

**a** = adjusted for age, sex, BMI, offspring-control status
**b = a +** for changes in all MRI and radiographic factors in the table

## 9.4 Discussion

This study documents the individual contributions of change in knee structures assessed on MRI and change in both JSN and osteophytes. Surprisingly, given JSN is currently being used as a surrogate measure for cartilage volume loss, change in meniscal tears showed a moderate correlation with both change in JSN and osteophytes. Change in meniscal extrusion and cartilage defects showed a slightly weaker correlation with JSN only, whereas direct measurement of cartilage volume loss showed no significant independent association with radiographic change (despite both worsening over the study timeframe).

Conventional radiographs are an unreliable method of evaluating articular cartilage loss in patients with early OA, as initial JSN is secondary to meniscal pathologies rather than thinning of articular cartilage in most cases [229]. Joint space is shared by both articular cartilage and meniscus. Damage to the meniscus either in the form of degenerative tears/extrusion [31] or mechanical removal [230, 231] will result in a decrease in the joint space. Previous cross-sectional studies have shown that the meniscus accounts for more of the variation in JSN than cartilage, however most of these changes are usually attributed to meniscal extrusion rather than tears [229]. Longitudinal studies[31, 111], conducted over 24-30 months, have shown that change in meniscal extrusion has a stronger association with JSN/JSW compared to tears and cartilage defects. In contrast, in our study, change in meniscal tears showed the strongest correlation with both JSN and osteophytes over 10 years and the two meniscal pathologies explained most of the change in JSN attributable to MRI structures, with cartilage defects showing only a weak but a significant correlation. There are a few possible explanations for stronger association of tears compared to extrusion. A recent study has shown that meniscal extrusion usually has an immediate effect on JSN, which does not progress much over time [111]. Furthermore, worsening of a meniscal tear, especially from a simple to a complex tear, will require a long follow-up period to observe these changes on MRI. This is perhaps why earlier studies with shorter follow-up periods failed to observe this association.

JSN is traditionally considered a surrogate marker for cartilage volume loss. Longitudinal studies, performed over shorter follow-up periods, have shown either moderate [232] or weak [111, 233] correlations between cartilage volume loss and change in JSN. We saw a similar

correlation between cartilage volume loss and JSN in unadjusted analysis but after adjustment for other knee structures there was virtually no correlation between the two over 10 years. A recent study by Crema *et al.* [212] showed that cartilage defects are the most common structural abnormality in people with worsening JSN. Our findings are in agreement with Crema *et al.* [212] but despite being more common than meniscal pathologies, change in cartilage defects only showed a modest but significant correlation with JSN. Our findings question the use of JSN as an outcome in chondro-protective drug trials as JSN is a poor reflection of cartilage volume loss in particular. Previous studies have shown that cartilage volume loss is a more sensitive and specific marker of cartilage integrity than JSN and possibly the best outcome measure for drug trials looking to preserve cartilage[111]. Moreover, cartilage defects have an unstable natural history as they can improve without any intervention depending on the age of the patient especially in people with less advanced disease [89, 141]. This is a possible explanation of weaker associations we observed in our study compared to previously available literature.

In terms of registration, radiographs are still the gold standard for OA trials [79]. The European and American regulatory agencies require evidence of not only an effect on JSN but also on pain and function as an end-point in DMOAD trials [234]. However, our data shows that change in JSN is mainly a reflection of change in meniscus, with cartilage defects showing only a weak, yet independent, correlation. Moreover, recent work from this cohort has shown that meniscal tear changes are strongly associated with cartilage volume loss, pain and function [211]. These findings suggest that meniscal tears are on the OA causal pathway and chondro-protective/DMOAD trials should account for the severity of meniscal tears to see the true effect of a certain drug on cartilage volume loss or changes in JSN.

We believe our findings are generalizable to a middle aged population. Although our cohort had a low prevalence of radiographic OA to begin with, we did not see any significant differences between participants with or without radiographic OA for any of the above-mentioned correlations. Similarly, we did not find any significant differences between the offspring and the controls either. Furthermore, our group has previously shown that change in meniscal extrusion has a stronger association with change in JSN compared to cartilage volume loss in a randomly selected older population as well [235]. Nevertheless, this finding merits replication in a sample purely with radiographic OA.

Our study has strengths and limitations. This study has the longest follow-up period of any OA study with global knee structural changes assessed on both MRI and radiographs. Radiographs and MRI scans for individual structures were assessed by independent readers, minimising the possibility of bias. A limitation of our study was a significant loss to follow-up over 10 years. Loss to follow-up can be a potential source of bias, however re-analysis of the data using inverse probability weighting did not change any of the results, indicating robust results. Another limitation of our study was the absence of meniscal tear scoring at the baseline visit, as we did not have the correct MRI sequence to score tears. However, the natural history data of meniscal tears in this cohort showed that none of the tears improved over 8 years, suggesting that meniscal tears present at visit-2 were likely to be present at baseline. This suggests that the association between radiographic and meniscal tear changes would have either remained the same over 8 (between visit-2 and 3) and 10 (visit-1 and 3) years or would have increased slightly if we had meniscal tears measurement at baseline, making the correlations we described even stronger [236, 237]. Lastly, tibial and femoral cartilage volume were segmented using different methodology as was outlined in the manuscript. Separate readers performed the measurements, which resulted in differences in how the scans were processed. Although both methods are almost equally sensitive at picking up any change in cartilage volume [158], this difference can still be a source of potential bias.

## Conclusion

Change in JSN is correlated with change in meniscal tears and, to a lesser extent, with meniscal extrusion and cartilage defects. In this sample change in JSN is a composite measure that does not reflect change in cartilage volume. These data, suggest that the use of JSN as an outcome measure in chondro-protective drug trials should be reviewed.

# CHAPTER TEN

## Summary and Future Direction

## 10.1 Summary

Osteoarthritis (OA) is the most common joint disorder in the world and in Western populations is one of the most frequent causes of pain, loss of function, and disability in adults [238]. The knee joint is the most commonly affected weight bearing joint by OA. Nearly one in two older adults are affected by knee OA by the age of 85 [33]. There is currently no cost-effective disease modifying osteoarthritic drugs available in the market. Most researchers have focused on the older adults with more established disease with little or no potential of reversibility. Hence it has been difficult to identify tissues with potential of reversibility that can be targeted in clinical trials. The aim of this thesis was to look at the long term natural history of knee structural changes in middle-aged adults, identify structures with potential for reversibility, and to examine the role of family history of disease in disease progression and predictors of early disease structural changes.

Chapter 4 examined the cross-sectional association between history of knee injury and knee structural damage assessed on MRI in middle-aged adults from the Offspring study and in a random community based sample of older adults. In middle-aged adults, BML presence, tibial bone area and meniscal extrusion presence were significantly higher in those with knee injury, whereas in older adults, cartilage defect presence, cartilage volume, BML presence and tibial bone area were significantly associated with knee injury. This was the first study to look at the association between history of knee injury and knee joint structural changes assessed on MRI and found that the association between knee injury and MRI-assessed structural pathology in the knee joint is moderate and appears to be stronger in older adults compared to middle-aged adults. However due to the cross-sectional design of the study, causation cannot be drawn from this data. A longitudinal study is warranted to further understand the role of knee injury and structural damage in different age groups.

Chapter 5 examined the role of family history of knee joint replacement due to OA and the risk of radiographic OA and cartilage volume loss over 10 years. Family history of knee OA increased the risk of radiographic OA (JSN and osteophytes) and medial tibial cartilage volume loss over 10 years compared to community-acquired controls with no family history of OA. Most of these changes were mediated by differences in baseline characteristics of offspring and controls except for increases in medial JSN.

Chapter 6 looked at the natural history of BMLs in middle-aged adults and found that the natural history of knee BMLs was unstable. BMLs were common in middle-aged adults at baseline. 24% of these BMLs at baseline increased in size, 55% remained stable and 21% decreased in size or resolved completely over 8 years. Change in BMLs was predicted by BMI and strenuous physical activity. An increase in BML size or a new BML resulted in an increase in pain especially in males and those with a family history of OA.

Chapter 7 examined the natural history of meniscal tears. Only 22% of the participants had a meniscal tear at baseline. Over 8 years, 16 % of the participants had an increase in severity of meniscal tears while none improved. Change in meniscal tears shared common risk factors with knee OA and was independently associated with worsening knee pain and structural damage suggesting that meniscal tears are on the knee OA causal pathway and not just a result of mechanical factors.

Chapter 8 looked at the natural history of cartilage defects. 44% of the participants had at least one cartilage defect at any site at baseline. Most of these defects remained stable, whereas 26% increased and 13% decreased in severity over 10 years. Cartilage defects independently predicted cartilage volume loss in the lateral compartment only. Change in cartilage defects on the other hand was associated with changes in BMLs and cartilage volume loss mostly in the lateral compartment, suggesting a more crucial role of cartilage defects in the development of lateral compartment knee OA. There was no independent association between change in cartilage defects and increase in pain after adjustment for BMLs, meniscal tears and effusion.

Chapter 9 examined the correlation between changes in structural abnormalities assessed on MRI and change in radiographic OA over 10 years. Change in JSN was correlated with change in meniscal tears and, to a lesser extent, with meniscal extrusion and cartilage defects. In this sample, change in JSN was a composite measure that did not reflect cartilage volume loss prompting the review of the use of JSN as an outcome measure in chondro-protective drug trials.

In conclusion, this series of related studies detail the natural history of knee structural progression in middle-aged adults. Structural changes such as BMLs and cartilage defects have the potential of reversibility in early disease and should be targeted in disease modifying

clinical trials. Meniscal tears and BMLs should be targeted in symptom modifying clinical trials especially in those with a family history of OA. Lastly findings from this thesis suggest that the use of JSN as an outcome measure in chondro-protective trial should be reviewed.

## 10.2 Future Direction

This thesis has presented several novel findings from a unique 10-year follow-up study of middle-aged adults. This thesis, and the Offspring study as a whole, has provided great insights into early knee OA structural changes. The most important aspect of this thesis is the detailed long-term knee structural natural history data, predictors of these changes and the structural changes/symptoms associated with these changes.

Several studies have shown the association between history of knee injury and radiographic OA [55, 123]. Chapter 4 was the first study that examined the association between history of knee injury and global knee structural pathologies. This study provided great insight as to how a knee injury early in life can predispose to structural damage in middle-aged and older adults. It suggests that history of knee injury can help identify people who are more predisposed to certain structural changes in different age groups. It may be possible to use knee injury history to identify fast progressors who can be targeted in clinical trials in order to slow disease progression and even prevent disease onset. Recently our group has finished data collection of a small longitudinal study in young Tasmanian Aussie Rules Footballers [239]. This study will examine the association between history of knee injury and structural and symptomatic changes over a full season and also compare it to the contralateral knee. Australian rules Footballers experience a high rate of injury and given the link between injury and future risk of OA, it is important to gain a better understanding of knee structural changes in athletes at high risk of injury. Data from this thesis highlighted that a previous history of knee injury was associated with MRI abnormalities in both middle and older adults. Given the clinical importance of knee injury, athletes who have had an injury or present with early structural changes on MRI may be a lucrative population to test early OA interventions. There may be scope to introduce therapeutic interventions into rehabilitation programs following joint injury that may have the potential to prevent knee OA in the future. Our group

is already in talks with Australian Football League (AFL) to carry out a larger study in professional footballers.

Chapter 5 and the subsequent chapters looking at the natural history of knee structures showed the crucial role family history of OA plays in the progression of disease. Having a family history of knee OA increases the risk of both JSN and cartilage loss over time. This highlights that this sub-group represents a potential group of patients who may particularly benefit from early OA interventions. It may be possible to target them for clinical trials targeting both structure and symptoms. Additionally, the data from this thesis has shown that the offspring not only had a higher prevalence of pain but also showed greater worsening over time. Data from chapters 6 and 7 suggests that having a family history of knee OA can also affect the pain perception pathway. Offspring participants had a higher increase in pain on the WOMAC scale per unit increase in severity of structural abnormalities including BMLs and meniscal tears. As the WOMAC pain scale is a subjective measure of pain, future studies could potentially use more objective measures of pain such as functional MRI scans to gain a better understanding of the influence of genes on pain perception. The relationship between reported pain intensity and the peripheral stimulus that evokes it depends on many factors such as the level of arousal, anxiety, depression, attention and expectation or anticipation. Pharmacological therapies such as anti-depressants and gabapentin can possibly target these pathways in the future for symptomatic relief.

Chapter 6 and 8 showed that BMLs and cartilage defects respectively have an unstable natural history and can regress in severity or completely heal. This suggests that these structures can be potentially targeted in disease modifying clinical trials. BMLs are especially an attractive target. Firstly, unlike cartilage defects, BMLs do not lose the ability to regress in older adults. Secondly changes BMLs are independently associated with changes in symptoms. Our group recently conducted a randomised controlled trial (RCT) examining the effectiveness of zoledronic acid (ZA) on knee pain and knee BMLs [189]. This study was a single centre double blind placebo controlled randomised trial of intravenous (IV) ZA (5 mg) vs placebo in 59 adults aged 50–80 years with knee pain (>40 mm on a visual analog score (VAS)) and a knee BML. We found that a single infusion of IV ZA was effective in reducing pain intensity and BML size compared to placebo after six months. A larger multi-centre trial is underway to further investigate the potential of this treatment. As discussed above,

treatments such as this one may be effective in younger populations who have had a knee injury, such as athletes, and are at an increased risk of developing future OA.

JSN is traditionally considered a surrogate marker for cartilage volume loss. Increase in JSN is the only method approved by regulators to register participants, monitor progression in disease-modifying OA drug (DMOAD) trials and is generally used as an end-point in chondro-protective trials. Data from chapter 9 suggests that JSN is a composite measure that reflects changes in meniscus mainly and to a lesser extent articular cartilage. Therefore it is not surprising that chondro-protective trials have thus far shown disappointing results using JSN as an outcome. Our findings form part of a large evidence base that is currently being used to demonstrate to the FDA that JSN is no longer an appropriate outcome in trials wanting to show a chondro-protective effect. Applications have been submitted to the FDA to have other structural outcomes measured on MRI (e.g. BMLs) be accepted as both an indication for therapy and an outcome measure in future trials. The success of such applications will hopefully be publically available soon.

In conclusion, data from this thesis detailed the long-term natural history of global knee structural changes in middle-aged adults. Data from this thesis identified the role of knee injury and structural knee damage in middle-aged and older adults. This data also emphasized the role of family history of knee OA in structural and symptomatic progression of the disease. BMLs and cartilage defects were identified as structures that have the potential to regress and can be potentially targeted in clinical trials. Lastly data from this thesis has questioned the use of JSN as an end-point in chondro-protective trials.

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**Appendix C.** Does cartilage volume measurement or radiographic osteoarthritis at baseline independently predict ten-year cartilage volume loss?

RESEARCH ARTICLE Open Access

# Does cartilage volume measurement or radiographic osteoarthritis at baseline independently predict ten-year cartilage volume loss?

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**Abstract**

**Background:** The aim of this study was to examine whether cartilage volume as measured by MRI and radiographic osteoarthritis (OA) at baseline predict cartilage volume loss over ten years independent of each other and other structural co-pathologies.

**Methods:** 219 participants [mean-age 45(26–61); 57 % female] were studied at baseline and ten years. Approximately half were the adult offspring of subjects who underwent knee replacement for OA and the remainder were randomly selected controls. Joint space narrowing (JSN) and osteophytes were assessed on radiographs and cartilage volume (tibiofemoral), cartilage defects, bone marrow lesions and meniscal tears/extrusion were assessed on MRI.

**Results:** Mean absolute and percentage per annum cartilage volume loss was 1284 $mm^3$ and 1.91 % respectively in the medial compartment and 1007 $mm^3$ and 1.38 % respectively in the lateral compartment. Higher baseline tibiofemoral cartilage volume was independently associated with greater absolute cartilage volume loss in both medial (β(95 % CI) = −300 (−399,−200)) and lateral (β = −338 (−443,−233)) compartments and percentage per annum loss in the lateral compartment(β = −0.15 (−0.29, −0.01)). Baseline JSN and osteophytes were associated with cartilage volume loss in the univariable analysis, however these associations did not persist after adjustment for other structural co-pathologies.

**Conclusion:** Cross-sectional cartilage volume measurement independently predicts cartilage volume loss over 10 years and can be used to identify fast progressors in clinical trials. Radiographic JSN and osteophytes on the other hand are a reflection of other co-pathologies assessed on MRI and do not independently predict cartilage volume loss over 10 years.

**Keywords:** Knee, Osteoarthritis, Cartilage volume, Magnetic resonance imaging, Radiographs

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## Background

Osteoarthritis (OA) is characterised by whole joint abnormalities including gradual cartilage volume loss [1]. Recent studies suggest that a cascade of structural changes occur in OA that involve sub-chondral bone expansion, bone marrow lesions (BMLs), meniscal tears, extrusion and eventually gradual loss of articular cartilage [1–7]. Loss of cartilage volume starts around the age of 40 years when radiographic changes are uncommon. [8] In early OA cartilage swelling appears to precede volume loss [6, 9]. This is supported by longitudinal evidence that higher baseline cartilage volume is associated with greater volume loss over a two-year period in early OA [2]. In patients with established OA, lower baseline cartilage volume appears to predict loss over a similar period [3].

Radiographic osteoarthritis (ROA) score has also been found to predict cartilage volume loss [10]. Whether this association is due to the presence of osteophytes or joint space narrowing (JSN) remains controversial. One study found that both JSN and osteophytes act as independent predictors of volume loss in a cohort of randomly selected older adults from community over a two-year period [10]. Other studies have shown that knees with definite osteophytes but without JSN do not show significantly greater rates of cartilage volume loss compared to healthy knees over a one-year period [11]. Similarly studies have shown that both presence [12, 13] and severity of ROA [11] is associated with cartilage thickness loss as well. To our knowledge no papers have looked at the association between ROA scores in early disease and volume loss over a ten-year period.

The aim of this study, therefore, was to examine whether cartilage volume as measured by MRI and ROA at baseline predict cartilage volume loss over ten years independent of each other and other structural co-pathologies.

## Methods

### Study subjects

This study was conducted as part of the Offspring study, which is an ongoing population-based study. The Offspring study began in southern Tasmania (primarily in the city of Hobart) in June 2000. Matched sampling was used to recruit the study participants (mean age 45 (26–61) years; 58 % females). Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000 [5]. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiographs when possible. The other half were age and sex matched controls, randomly selected from the population with no history of knee OA in either parent. Controls were randomly selected from the electoral roll in southern Tasmania (population 229,000), a comprehensive population listing. This study includes data from the baseline visit, 2 year and 10 year follow up.

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants. Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). Participants were also excluded if they had undergone a knee replacement surgery or did so after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

### Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$).

## Magnetic resonance imaging

MRI of the right knee was performed as described previously [14–16]. All knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Picker International, USA) using a commercial transmit-receive extremity coil. The following image sequence was used: (i) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 msec, echo time 12 msec, field of view 16 cm, 60 partitions, 512 × 512-pixel matrix, slice thickness of 1.5 mm without an interslice-gap; and (ii) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256 × 256 matrix, slice thickness of 4 mm with an interslice gap of 0.5–1.0 mm.

### Cartilage volume assessment

Knee cartilage volume was evaluated at baseline and 10 years by a trained observer on T1-weighted gradient echo MR images. Knee cartilage volume was determined by means of image processing on an independent workstation at baseline and follow up. The volumes of individual cartilage plates (medial tibia and femora, and lateral tibia and femora) were isolated from the total volume by manually drawing dis-articulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 × 312 μm by 1.5 mm thickness, continuous sections) for the final three-dimensional rendering to calculate the cartilage volume.

Tibial cartilage volume was assessed using Osiris (University of Geneva, Switzerland) software as previously described [14, 17]. The coefficient of variation(CV) ranged from 2.1 to 2.2 % for intra-observer repeatability [18]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Canada), as previously described [19, 20]. The CV was approximately 2 % for intra-observer and inter-scan repeatability [20]. Total cartilage volume was calculated as: tibial + femoral cartilage volume.

Absolute cartilage volume loss was calculated as: follow-up total cartilage volume − baseline total cartilage volume. Percentage per annum cartilage volume loss was calculated as: ((absolute cartilage volume loss/baseline cartilage volume)/time period between MRI acquisition at baseline and visit-3) × 100.

### Cartilage defects

Cartilage defects were assessed at baseline and 10 years on T1-weighted gradient echo MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites on a 0–4 scale, as previously described [16]: grade 0 = normal cartilage; grade 1 = focal blistering and intracartilaginous low-signal intensity area with an intact surface and base; grade 2 = irregularities on the surface or base and loss of thickness <50 %; grade 3 = deep ulceration with loss of thickness >50 %; and grade 4 = full-thickness chondral wear with exposure of subchondral bone. Intraobserver reliability (expressed as intraclass correlation coefficient (ICC)) ranged from 0.89 to 0.90. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.85–0.90 [16].

### Meniscal tears

Meniscal tears were assessed by a trained observer on T1-weighted gradient echo and T2-weighted (side by side) MR images at visit-2 and 3 of the study as previously described [19]. The proportion of the menisci affected by a tear was scored separately (0–2 scale; 0 = absence of a tear, 1 = simple tear of different types: longitudinal, oblique, radial or horizontal, 2 = complex tear signifying loss > 50 % area of meniscal tissue) at the anterior, middle, and posterior horns (medially/laterally). Anterior, middle and posterior scores were summed to get medial and lateral meniscal tear scores. The intra- and inter-observer correlation coefficient ranged from 0.86 to 0.96 [20]. Meniscal tears were scored at visit-2 of the Offspring study, 2 years after the baseline visit.

### Meniscal extrusion

Meniscal extrusion was assessed by a trained observer on T1-weighted gradient echo MR images at baseline and 10 years as previously described [19]. The proportion of the menisci affected by a partial or full extrusion was scored separately (yes/no) at the anterior, middle, and posterior horns (medially/laterally). Anterior, middle and posterior scores were summed to get medial and lateral meniscal tear/extrusion scores. The intra- and inter-observer correlation coefficient ranged from 0.85 to 0.92 for meniscal extrusion [20].

### Bone marrow lesions

Bone marrow lesions (BMLs) were assessed on fat suppressed T2-weighted MR images as described previously [21]. BMLs were defined as areas of increased signal intensity in the subchondral bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patellar and inferior patellar sites. One trained observer scored the BMLs by measuring the maximum area of the lesion in a specific compartment. The observer manually selected the MRI slice with the greatest BML size. The BML with the highest score was used if more than one lesion was present at the same site. The ICC was 0.97. BMLs were scored at visit-2 of the Offspring study, 2 years after the baseline visit.

## Radiography

A standing anteroposterior semiflexed x-ray of the right knee was taken in all subjects at baseline and 10 years. The angle was kept to 10–15° by a purpose built goniometer. The tube to film and tube to tibial plateau angle was 90°. Daily quality assurance was performed on the equipment. Radiographs were scored individually for osteophytes and joint space narrowing (JSN), as described previously [22]. Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial JSN, lateral JSN, medial osteophytes (femoral and tibial combined) and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers (LC, AM) simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International (OARSI) atlas [23]. ROA score was calculated by adding JSN (medial and lateral sites) and osteophytes (medial and lateral tibial and femoral sites) scores. A non-zero score in either JSN or osteophytosis was regarded as evidence of any ROA. Total ROA score had a possible range of 0–18. Reproducibility was assessed in 50 radiographs, two weeks apart, and yielded an agreement (linear weighted kappa value) of 0.87–1.00 for osteophytes and 0.94–1.00 for JSN ($p$-value < 0.001).

Readers for all the scans were either musculoskeletal radiologists with several years of experience in OA research or health professionals trained by musculoskeletal radiologists. Readers were not blinded to the chronological sequence of the radiographs and MRI scans.

## Statistical analysis

T-tests and chi-square tests were used to compare differences in means and proportions as appropriate when

examining demographic, cartilage volume and radiographic data. Baseline characteristics of the participants were split into two groups for comparison using mean total cartilage volume loss (absolute) over 10 years: (i) less than mean total cartilage volume loss; (ii) greater than or equal to mean total cartilage volume loss.

Linear regression analysis was used to examine the association between baseline radiographic structures/cartilage and cartilage volume loss (absolute and percentage) over 10 years. β-coefficients were standardised to describe the association between baseline radiographic structures/cartilage volume and cartilage volume loss, so that cartilage volume loss was expressed as loss per standard deviation change in the predictor variables [21, 24, 25]. Multivariable analysis was adjusted for age, sex, BMI, offspring-control status, radiographic structures/cartilage volume at baseline and MRI structures which had a higher prevalence (or showed a similar trend) in participants with greater than or equal to mean total cartilage volume loss. All the associations between baseline JSN and cartilage loss were adjusted for baseline osteophytes and vice versa. Interactions terms were calculated to examine significant differences between the offspring and control groups.

Further sub-analyses looking at the association between baseline cartilage volume and/or ROA and absolute cartilage volume loss stratified by mean age was performed to look at the effect of advancing age on the associations described in the study.

To counter the effect of regression to the mean/tracking, when describing the association between baseline cartilage volume and cartilage volume loss, further sub-group analysis was done with baseline cartilage volume stratified by the mean value.

A *P*-value of less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 12.0 for windows (StataCorp LP).

## Results

Of the 371 participants included in the Offspring study, 219 between the ages of 26 and 61 years were followed up after 10 years. The characteristics of participants who were followed up compared to participants who were lost to follow up were as follows, respectively: age: 45.25 (±6.67) vs 45.07 (±7.15) years, $p = 0.806$; female sex: 57 % vs 59 %, $p = 0.749$; BMI: 27.2 (±4.96) vs 26.8 (±4.31), $p = 0.499$; offspring 52 % vs 47 %, $p = 0.891$; knee ROA: 18 % vs 15 %, $p = 0.486$ and total tibiofemoral cartilage volume at baseline ($mm^3$): 14199 (±3463) vs 14113 (±3410), $p = 0.611$.

Table 1 describes the baseline characteristics of the group stratified by the mean total cartilage volume loss over 10 years. The average age of the cohort was 45 years. Participants with greater than the mean absolute volume loss were significantly older, had a significantly lower percentage of male participants, a significantly higher prevalence of medial JSN, medial osteophytes and any meniscal tear, and a higher medial and lateral tibiofemoral cartilage volume at baseline visit.

Both absolute and percentage per annum cartilage volume loss were higher in the medial tibiofemoral compartment compared to the lateral tibiofemoral compartment. Mean absolute and percentage per annum cartilage

**Table 1** Baseline characteristics of participants split by total (tibiofemoral) cartilage loss (absolute) over 10 years [a]

| | Total volume loss <16 % (n = 109) | Total volume loss ≥16 % (n = 110) | P-Value |
|---|---|---|---|
| Age (years) | **44.2(6.9)** | **46.2(6.6)** | **0.038** |
| Males (%) | **69** | **45** | **0.001** |
| BMI | 26.8(4.4) | 27.3(5.2) | 0.449 |
| Any medial JSN (%) | **8** | **20** | **0.015** |
| Any lateral JSN (%) | 2 | 3 | 0.659 |
| Any medial osteophytes (%) | **3** | **12** | **0.016** |
| Any lateral osteophytes (%) | 5 | 6 | 0.770 |
| Medial (tibiofemoral) cartilage volume ($mm^3$) | **6098 (1431)** | **7435 (1583)** | **<0.001** |
| Lateral (tibiofemoral) cartilage volume ($mm^3$) | **6577 (1716)** | **7969 (1757)** | **<0.001** |
| Total (tibiofemoral) cartilage defects (mean) | 4.0 (1.0) | 3.9 (1.3) | 0.674 |
| Any meniscal tear (%) | **13** | **31** | **0.005** |
| Any meniscal extrusion (%) | 5 | 15 | 0.079 |
| Any (tibiofemoral) BMLs (%) | 54 | 50 | 0.597 |

[a]Mean (SD) except for percentages. *P*-values determined by t-test or $\chi^2$ test (where appropriate)
Bold font signifies statistically significant results

volume loss was 1284 $mm^3$ and 1.91 % respectively in the medial compartment and 1007 $mm^3$ and 1.38 % respectively in the lateral compartment.

Figure 1a describes the association between baseline tibiofemoral cartilage volume and absolute cartilage volume loss. A higher baseline cartilage volume was associated with higher absolute cartilage volume loss over 10 years. Figure 1b describes the association between baseline ROA score and absolute cartilage volume loss. ROA score ranged from 0 to 6 (possible range 0–18) in the study population at the baseline visit. A higher baseline ROA score was associated with higher absolute cartilage volume loss on average over 10 years.

Table 2 describes the association between the baseline tibiofemoral cartilage volume and cartilage volume loss over 10 years. Baseline cartilage volume was significantly associated with absolute cartilage volume loss over 10 years in both compartments in the multivariable analysis. Further adjustment for cartilage defects and BMLs did not change the effect size considerably. There was a similar trend for the association between the baseline tibiofemoral cartilage volume and percentage per annum cartilage volume loss but the association reached statistical significance in the lateral compartment only (β (95 % CI) = −0.15 (−0.29, −0.02), $p = 0.01$) in the fully adjusted model.

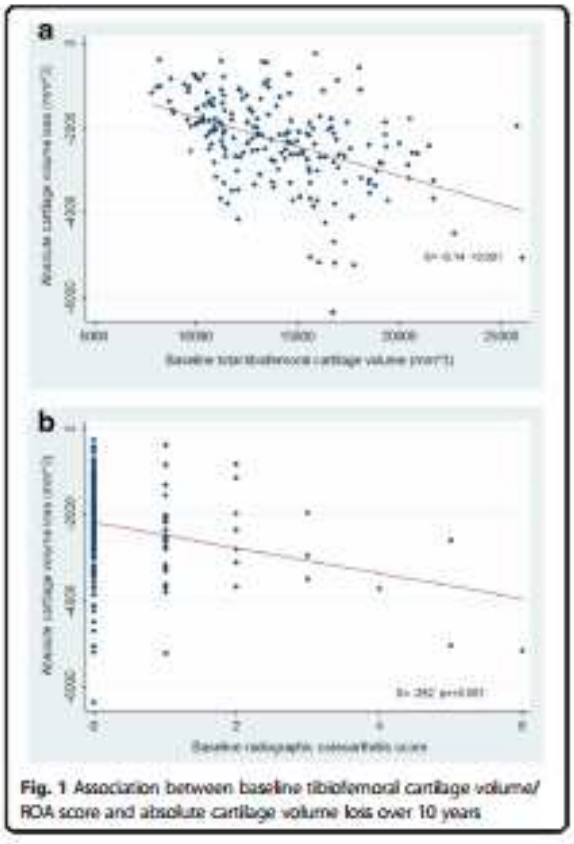


**Fig. 1** Association between baseline tibiofemoral cartilage volume/ROA score and absolute cartilage volume loss over 10 years

**Table 2** Association between baseline cartilage volume and cartilage volume loss over 10 years

| Baseline cartilage volume (size) | Unadjusted β (95 % CI) | Adjusted* β (95 % CI) |
|---|---|---|
| Medial (tibiofemoral) cartilage volume loss (absolute) | | |
| Medial tibiofemoral (per SD) | **−265 (−337,−194)** | **−300 (−399,−200)** |
| Lateral (tibiofemoral) cartilage volume loss (absolute) | | |
| Lateral tibiofemoral (per SD) | **−226 (−303,−148)** | **−338 (−443,−233)** |

*Adjusted for age, sex, BMI, offspring-control status, ROA at baseline, meniscal tears at visit-2 and meniscal extrusion at baseline where appropriate
SD Standard deviation
**Bold** denotes significant results

Sub-group analysis was done to describe the association between baseline cartilage volume stratified by mean volume and absolute cartilage volume loss over 10 years. Both greater than or equal to the mean total tibiofemoral cartilage volume (β (95 % CI) = −744 (−1162, −325)) and less than mean cartilage volume (β (95 % CI) = −423 (−837, −9)) significantly predicted cartilage volume loss in the fully adjusted model.

Table 3 describes the association between the baseline radiographic measures and cartilage volume loss over 10 years. There were significant associations between medial JSN, lateral JSN and osteophyte scores at baseline and compartment specific absolute cartilage volume loss in the unadjusted analysis. However, none of these associations persisted in the multivariable analysis. Similarly there were no significant associations between the baseline radiographic measures and percentage per annum cartilage volume loss in either the unadjusted or the fully adjusted models.

Further sub-analyses looking at the association between baseline cartilage volume and/or ROA and absolute cartilage volume loss stratified by mean age showed no significant differences between the two age groups

**Table 3** Association between baseline radiographic measures and cartilage volume change over 10 years

| Baseline radiographic measure | Unadjusted β (95 % CI) | Adjusted* β (95 % CI) |
|---|---|---|
| Medial (tibiofemoral) cartilage volume loss (absolute) | | |
| Medial JSN (per SD) | **−124 (−204,−43)** | −77 (−170,+14) |
| Medial osteophytes (per SD) | −71 (−150,+8.9) | +61 (−20,+143) |
| Lateral (tibiofemoral) cartilage volume loss (absolute) | | |
| Lateral JSN (per SD) | **−80 (−158,−2)** | −21 (−109,+67) |
| Lateral osteophytes (per SD) | **−172 (−246,−97)** | −72 (−175,+32) |

*Adjusted for age, sex, BMI, offspring-control status, cartilage volume at baseline, meniscal tears at visit-2 and meniscal extrusion at baseline and/or JSN and osteophytes at baseline where appropriate
SD Standard deviation
**Bold** denotes significant results

except for a significantly stronger association between baseline cartilage volume and cartilage volume loss over 10 years in the lateral compartment only in the older participants. Participants with mean age ≥45 years showed a significant association (β = −405 (−558, −252)) between the baseline lateral tibiofemoral cartilage volume and cartilage volume loss, whereas participants with mean age <45 years showed no significant association (β = −173 (−387, +41)).

Analyses to explore interactions between the offspring and control groups found no statistically significant difference between the two groups for any of the associations described above. The association between baseline cartilage volume and cartilage volume loss were statistically significant in both the offspring and controls groups when analysed separately (data not shown).

## Discussion

This longitudinal study documents the associations between baseline cartilage volume/ROA and cartilage volume loss over 10 years. Mean absolute and percentage per annum cartilage volume loss was substantial (19.1 % and 13.8 % in the medial and lateral compartments over 10 years) but less than that seen in older populations [8]. Higher baseline tibiofemoral cartilage volume independently predicted greater absolute cartilage volume loss in both compartments and percentage per annum loss in the lateral compartment only. Baseline JSN and osteophytes did not independently predict absolute or percentage per annum cartilage volume loss in either compartment.

This is the first study to describe an independent association between baseline cartilage volume and absolute cartilage volume loss over 10 years. Some recent studies have shown similar associations between baseline cartilage volume and cartilage volume loss over shorter timeframes but none of these studies accounted for knee structural abnormalities such as meniscal tears, meniscal extrusion and BMLs [2, 26, 27]. All of these structures have been shown to predict cartilage volume loss [28] and are potential confounders for the associations described in this study. The association was independent of these factors in the current study. Furthermore, none of the studies mentioned above described the association between the baseline cartilage volume and cartilage volume loss for both tibial and femoral sites.

A criticism of identifying people who will lose more cartilage using the baseline cartilage volume is that association could be due to regression to the mean/tracking. Regression to the mean is a statistical phenomenon that can make natural variation in repeated data look like real change [29]. It happens when unusually large or small measurements tend to be followed by measurements that are closer to the mean. Unusually high or low cartilage volume to begin with could be due to a number of factors such as cartilage random variation due to body size, sex and co-pathologies. To counter the effect of regression to the mean, further sub-group analysis was done with baseline cartilage volume stratified by the mean value. Both group showed a significant association between the baseline cartilage volume and cartilage volume loss, albeit with a greater effect size in participants with a higher baseline cartilage volume. This suggests that the significant association we described is not solely due to regression to the mean. Similar independent association in the lateral compartment for percentage per annum loss, which also takes into account the cartilage volume to begin with, also suggests that this association is real. However, we did not see any independent associations for medial compartment percentage per annum loss suggesting there is an increase in cartilage volume, due to cartilage swelling, that precedes cartilage volume loss in early OA [7]. Early OA is characterised by matrix changes including a reduction in cellular and proteoglycan content and subsequent water retention and proteoglycan dilution [30]. This depletion of proteoglycan matrix has been closely related to the progression of OA [9]. The swelling of cartilage, in the form of increased volume [9], detected by MRI in early OA has been shown to correlate with depletion proteoglycan matrix and cartilage volume loss, and would explain the associations described in this study.

Few longitudinal studies have looked at the association between baseline ROA and cartilage volume loss and to date, they have shown mixed results. Preliminary cross-sectional findings published from this cohort showed that JSN but not osteophytes were associated with a decreased tibial cartilage volume [18]. Similarly Saunders et al. [10] examined the relationship in a randomly selected older cohort over three years and found that JSN and osteophytes both predicted volume loss in a dose response manner but did not adjust for potential confounders such as meniscal tears/extrusion and BMLs. Furthermore, studies looking at the association between JSN and cartilage thickness loss have shown mixed results as well [20, 31], possibly due to different study populations and shorter follow-up periods. Univariable analysis looking at the association between baseline ROA and cartilage volume loss from our 10 year data showed similar results to Saunders et al. [10] but none of these associations persisted once adjusted for MRI assessed co-pathologies. JSN is a composite of structures that are not visible on radiographs. Variation in JSN and longitudinal changes are a reflection of changes in cartilage and meniscus [32]. Hence when adjusted for abnormalities in these structures, JSN did not independently

predict cartilage volume loss. Osteophytes are considered an instigating factor in OA causal pathway and studies have shown that presence of osteophytes is associated with a higher prevalence of cartilage defects and decreased cartilage volume. However, once adjusted for co-pathologies, osteophytes failed to independently predict cartilage volume loss in either compartment. Recent studies have suggested that loss of meniscal function is associated with both cartilage volume loss and presence of osteophytes due to increased bio-mechanical stress on the underlying cartilage and the bone. These results and the data from the present study suggest that osteophytes may be on the OA causal pathway or an attempt at repair and are probably not an independent instigating factor for early cartilage volume loss.

Rate of cartilage volume loss and OA progression varies from patient to patient. Cartilage volume loss is often the end-point in chondro-protective drug trials and has been shown to predict total knee replacement surgery [22]. It is imperative for chondro-protective trials to identify fast progressors to make these trials more responsive and sensitive to change. Previous studies have suggested that degree of JSN can be used to identify the sub-groups, which will lose cartilage faster in chondro-protective drug trials [31]. However, data from this study shows that JSN is not an independent predictor of cartilage volume loss. On the other hand, our results suggest that cartilage volume to begin with can be used to identify fast progressors especially if we can differentiate between swollen and non-swollen cartilage.

The key strength of this study is the long follow up period. To our knowledge this study has the longest follow up period using MRI to monitor disease progression in OA. Another strength is that we examined both femoral and tibial cartilage volume loss whereas previous studies have often only reported on one or the other. Lastly, adjustment for other MRI structural co-pathologies points towards the mediating mechanisms involved in cartilage volume loss. This study has a number of limitations as well. First, around 40 % of participants were lost to follow up at ten years. Those lost to follow-up however were found to be similar in terms of baseline characteristics compared to the participants who were followed-up. Secondly we examined a specific middle-aged group and therefore the results cannot be generalised to the entire population especially people with advanced OA. We believe our results are generalisable to a middle-aged population as we did not see any significant differences between the offspring and control groups for any of the associations described in this study. Third, meniscal tears and BMLs were scored at two years and not at the baseline visit. However changes in these structures over 8 years was small suggesting that these are unlikely to change the effect size considerably.

## Conclusion

Cross-sectional cartilage volume measurement independently predicts cartilage volume loss over 10 years and can be used to identify fast progressors in clinical trials. Radiographic JSN and osteophytes on the other hand are a reflection of other co-pathologies assessed on MRI and do not independently predict cartilage volume loss over 10 years.

### Competing interests

Jean-Pierre Pelletier and Johanne Martel Pelletier are shareholders in ArthroLab Inc; the other authors declare no completing interests.
All authors have completed the Unified Competing Interest form (available on request from the corresponding author).

### Authors' contributions

AM was responsible for data collection, preparation of initial manuscript and revisions of the manuscript. HK was responsible for the analysis and interpretation of data, preparation of initial manuscript and revisions of the manuscript. DA was responsible for data cleaning and management, data interpretation and drafting of the manuscript. LC was responsible for data collection and drafting of the manuscript. LB was responsible for data analysis and drafting of the manuscript. JPP and JMP were responsible for the measurements of femoral cartilage volume, meniscal tears and meniscal extrusion, and drafting of the manuscript. CD, FC, and GJ were responsible for protocol development, data acquisition and drafting of the manuscript. All authors read and approved the final manuscript.

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